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EPIDEMIOLOGY OF DIARRHOEA AND IRRITABLE BOWEL SYNDROME AMONG TRAVELLERS

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ABBREVIATIONS AND NOTATIONS

TD	Travellers' diarrhoea
IBS	Irritable Bowel Syndrome
pIBS	postinfectious Irritable Bowel Syndrome
FGID	Functional Gastrointestinal Diseases
VFR	Visiting Friends and Relatives
RR	Risk Ratio
CI	Confidence Interval
MD	Medical Doctor

BACKGROUND AND PURPOSE

About 80 million international travellers from high income countries per year cross the borders of tropical countries and a lot will encounter travellers' diarrhoea as its' notoriety and various studies from the past suggest: Travellers' diarrhoea (TD) affects up to 60% of persons during a two week stay in a high risk country such as India or Kenya (1, 2) as illustrated in Figure 1. It is an old disease formerly known predominantly among soldiers who appeared to suffer more from diarrhoea and dysentery than from injuries of war (3). Abundance of colloquial terms may be as frequent as the disease itself and the names usually bear regional or historical flags, to name a few: Montezumas' Revenge, *la venganza de Atahualpa*, Delhi Belly, Cairo Two-Step...

Besides incapacitating travellers abroad or shortly after return, early studies indicated that diarrhoea could persist for one month or longer in 0.9% of travellers (1, 4). More recently, Irritable Bowel Syndrome (IBS) has been described among 6 of 61 (10%) previously healthy U.S. students who had experienced TD in Mexico (5). Since this study was limited to a small number of young people in one single country a broader assessment of sequelae of TD is desired.

IBS as one of over 20 functional gastrointestinal disorders (FGID) is characterized by a wide variety of persistent symptoms. Symptoms can be multiple and change over the time. In western societies up to 14 % meet any diagnostic criteria and IBS prevalence ranges from 3 to 10% depending on region and diagnostic criteria (6-8). Symptoms include abdominal discomfort or pain associated with defecation or a change in bowel habit and with features of disordered defecation. In absence of any clear organic cause the pathogenesis of IBS is considered to be multi-factorial. Overlapping psychological factors, altered visceral pain perception and abnormal gastrointestinal motility or permeability have been postulated as predominant mechanisms (9). Altered interaction between the immune and neuroenteric system caused by chronic, low-grade mucosal inflammation may lead to visceral hypersensitivity. Infectious gastroenteritis is discussed to initiate this inflammatory response (9-11). Several studies suggest that recent gastroenteritis (such as TD) might be one of the strongest risk factors for developing postinfectious IBS (pIBS) (5, 12, 13). A strong association between TD and the subsequent developing of IBS may have important implications for public health strategies at preventing TD and for planning interventions to protect travellers at great length. Therefore we first need to know updated TD rates and secondly we can focus on it's consequences, in this case IBS. Finally we will compare rates and risk factors found with previous data of travellers for a broader assessment of health impairments abroad.

SUMMARY

Travellers' diarrhoea (TD) is the most common disease contracted when visiting tropical destinations. Irritable Bowel Syndrome is characterized by a variety of persistent symptoms. Symptoms can be multiple and change over the time. In western societies prevalence ranges from 3 to 10%, depending on region and diagnostic criteria. Symptoms include abdominal discomfort or pain associated with defecation or a change in bowel habit and with features of disordered defecation. Recent gastroenteritis (such as travellers' diarrhoea) might be one of the strongest risk factors for developing postinfectious Irritable Bowel Syndrome. Previous smaller studies have detected rates of 4 to 11% of Irritable Bowel Syndrome among travellers to low income countries. So far no survey investigated this risk in Europeans, none used the Rome III diagnostic criteria.

Within the same cohort of travellers we first address TD attack and incidence rates and TD-associated risk factors (chapter I), secondly we concentrate on IBS attack, incidence rates and risk factors (chapter II) and finally, we compare our prospective cohort study established in chapter I and II with a similar cohort and with a retrospective study design focusing on selected health problems abroad, diarrhoea included (chapter III).

We performed a prospective cohort study including follow-up six months post travel to a high TD risk region (confer Figure 1). All study participants were recruited at the *Zentrum für Reisemedizin* of the University of Zurich. Inclusion and exclusion criteria were strictly defined. A self-administered first questionnaire (Q1) was to be collected at enrolment. A second questionnaire (Q2) was sent immediately post - travel. After six months travellers received the final questionnaire (Q3) to identify persistent gastrointestinal problems. We adopted the following case definitions for TD and IBS. TD consisted of 3 or more unformed stools per 24h with or without an additional symptom. The IBS diagnosis was based on the Rome III criteria. IBS positives got the opportunity to receive a first free counselling by the Division of Gastroenterology of the University Hospital of Zurich.

Data were analyzed by statistical standard methods including descriptive analysis, incidence rates calculation, univariate and multivariate analysis, calculation of risk ratios (RR) and 95% confidence intervals, adjustment of confounding, multivariate analysis using logistic regression and sensitivity analyses to check on robustness of estimates.

The study protocol has been approved by the Ethical Commission of the Canton of Zurich.

In **chapter I** we found the TD attack rate to be 34.4% (95%CI 32.6-36.1), the overall two-weeks incidence 27.2% (95%CI 26.1-28.8). Among the 3100 recruited, 2800 could be investigated, resulting in a participation rate of 89.2%. The highest two-weeks incidence rates were found for West Africa (45.5%; 95%CI 37.6-53.5) and the Indian subcontinent (35.5%; 95%CI 31.2-39.8). Median TD duration was 2 days (range 1-90). Multivariate logistic regression analysis for detecting the most prominent risk factors of TD showed that a resolved diarrhoeal episode experienced in the 4 months pre-travel (RR 2.04, 95%CI 1.59-2.61), antidepressive comedication (RR 2.10; 95%CI 1.16-3.78), allergic asthma (RR 1.67; 95%CI 1.10-2.54), and reporting TD-independent fever (RR 6.56; 95%CI 3.07-14.06) are all significant potential contributors. TD remains a frequent, usually self-limited travel disease. Patients with pre-travel diarrhoea more often develop TD while abroad. Other clinically relevant risk factors like allergic asthma in the patients' history will need in future more detailed research. A French group (Benard et al.) for example suggested in absorption studies with chromium 51-labelled EDTA a permeability defect of the gastrointestinal tract in asthmatic patients, supporting the hypothesis of the so called "united mucosa" characterised by defects in the whole mucosa.

Among 2476 study participants with follow-up (79.9%) 6 months post-travel of the initial cohort of chapter I resulted in 38 (1.5%) subjects with Irritable Bowel Syndrome (IBS) as described in **chapter II**. The date 6 months after return of the index travel was the study endpoint. The 6 months-IBS incidence rate was 1.5% (1.1-2.0 95% CI), the postinfectious 6 months-IBS incidence rate 3.0% (1.9-4.2 95% CI). In a multivariate logistic regression analysis we found the following risk factors: Suffering from travellers' diarrhoea abroad (RR 3.67; 95% CI 1.82-7.61), an adverse life event experienced within 12 months pre-travel (RR 3.11; 95%CI 1.43-6.78), a diarrhoea episode experienced up to 4 months pre-travel (RR 2.74; 95%CI 1.34-5.61). In a large population of Swiss travellers IBS had a lower incidence rate as compared to previous studies among international travellers and within community-based studies. Nevertheless IBS is an important long-term travel sequelae with its incidence rate similar to influenza, but with a different prognosis. Strategies targeted at risk-groups need to be developed including more IBS cases to allow detailed sub-group analyses.

Chapter III gives an overview of selected and frequent health problems abroad. We compare two prospective cohort studies (the IBS cohort of chapter II; cohort A), a previous one of the Travel Health Centre Zurich research group (cohort B; years 1998 – 2000) and a retrospective Swiss dataset including ill-returned travellers with data collected from 2004 to 2005 and published in 2007.

43% (cohort A) and 40% (cohort B) reported any illness abroad, most frequent were diarrhoea (attack rate A 34.4% and B 25.9%) and cold (A 10.2%; B 16.8%). 5.3% A and 10.1% B measured fever. In both cohorts travellers suffering from health problems abroad tended to be younger (RR age A (18-25 years) 1.53; 95%CI 1.12-2.09 and B (12-25 years) 1.12; 95%CI 0.85-1.47), stayed longer abroad (RR weeks of stay A 1.27; 95%CI 1.20-1.36 and B 1.08; 95%CI 1.05-1.11) and had more frequently visited the Indian subcontinent (RR A 1.79; 95%CI 1.38-2.34 and B 2.07; 95%CI 1.36-3.16). Females reported significantly more constipation and insect stings, male travellers suffered more from fever. Within the retrospective dataset travel durations were shorter and visiting friends and relatives accounted for one third of the study population with a different risk pattern for infectious diseases when compared to the prospective cohorts. Fever and gastrointestinal diseases were also frequently

reported diseases among the retrospectively collected patients, but with lower acute diarrhoea rates among visiting friends and relatives. Whereas other illnesses such as malaria, sexually transmitted diseases and neglected tropical diseases (e.g. Leishmaniasis) formed together the biggest entity, such proportions were out of reach in cohort studies.

Diarrhoea is a frequent infectious disease encountered abroad. In future we will need more specific risk group assessment for prevention and prophylactic interventions must be evaluated.

Prospectively collected questionnaire–based results and data evaluated on the basis of MD diagnoses complement each another. Prospective cohort studies strengths' is the exposure assessment. They summarise encountered health problems abroad, assess incidence rates and risk ratios in generally healthy travellers with pre- and post-travel exposure factors. Limiting factor is – if the study is questionnaire based – a reliable and accurate case definition and the further evaluation. Retrospective case series base on MD diagnosis, they focus on more serious or persistent health care problems after travel exposure. Their weakness is that the exposure assessment is often prone to bias.

GERMAN SUMMARY - ZUSAMMENFASSUNG

Diese Studie hat primär zum Ziel, Charakteristika von Reisedurchfall (Kapitel I), des Reizdarm-Syndroms (Kapitel II) sowie die ausgewählten, häufigsten, generellen Reisekrankheiten (Kapitel III) qualitativ und quantitativ zu beschreiben. In diesem letzten Schritt wurde die Primärstudie von Kapitel I und II, eine prospektive Kohortenstudie, mit einer anderen ebenfalls prospektiven Kohortenstudie früherer Zeit und einer retrospektiven Schweizer GeoSentinel Studie verglichen.

Reisediarrhöe ist bei Erwachsenen die mit Abstand häufigste Gesundheitsstörung auf Reisen in subtropische und tropische Destinationen. Reisediarrhöe, definiert als ≥ 3 ungeformte Stuhlgänge pro 24 Stunden, wird oft begleitet von Symptomen wie Spasmen, Meteorismus, Nausea, Fieber, plötzlichem Stuhldrang, Erbrechen und Blut oder Schleim im Stuhl; Verursacher sind fäkal-oral übertragene Bakterien, Viren oder Parasiten. Reisediarrhöe schränkt die Mobilität erheblich ein, ist jedoch selten lebensbedrohlich. In den meisten Fällen heilt sie spontan nach etwa 4 Tagen. Bei einer Minderheit können allerdings Symptome anhalten und eine chronisch - fluktuierende Folgeerkrankung auslösen: das Reizdarmsyndrom.

Das Reizdarmsyndrom gehört zu den häufigsten funktionellen Magen-Darm-Erkrankungen. Es definiert sich durch regelmässige Abdominalschmerzen und Änderung der Stuhlgewohnheiten. Die Diagnosegrundlage stellen die Rome III Kriterien (*Rome Foundation*, Prof. Dr. med. D. A. Drossman, Begründer) dar.

Ein Schwerpunkt dieser Studie liegt bei der Evaluation des potentiellen Zusammenhangs von Reisedurchfall und nachfolgend auftretendem Reizdarm-Syndrom. In der Literatur ist bekannt, dass Enteropathogene eine initiierende Rolle bei chronischen Darmerkrankungen innehaben. In vorhergehenden Studien mit Reisenden waren die Stichprobenzahlen klein. Zum Themenkomplex, der durch Infektionen verursachten chronischen Erkrankungen, wird mit diesem breit angelegten Forschungsprojekt ein wichtiger Beitrag geliefert, wobei Risikogruppen identifiziert und neue Strategien in der Prävention evaluiert werden können.

Eine Kohorte von Reisenden wird prospektiv mittels Fragebogen vor, während und einmal nach der Reise befragt. Insgesamt sollen ca. 2500 Reisende rekrutiert werden. Neuerkrankten (mit vermutetem Reizdarmsyndrom) wird eine unentgeltliche Beratung in der Gastroenterologie des Universitätsspitals Zürichs angeboten. Um die Antwortquote zu erhöhen, wird eine kleine Verlosung von Reisegutscheinen am Ende der Studie durchgeführt. Fragebögen umfassen standardisierte Fragen, gemäss den Rome III-Kriterien für Reizdarm. Geschlossene, strukturierte Fragen zur Demografie, zu reise-, verhaltens- und gesundheitsbezogenen Faktoren in Anlehnung an den staatlichen Schweizerischen Gesundheitsfragebogen und erprobten Reisediarrhöestudien sind ebenfalls Teil der Forschungsstudie.

Datenauswertung. Die erfassten Faktoren werden qualitativ und quantitativ beschrieben. Inzidenzraten und 95% Konfidenzintervalle werden berechnet. Multiple Regressionsmodelle werden eingesetzt, um den Zusammenhang zwischen Reisedurchfall und Reizdarm zu evaluieren. Zwecks Prüfung der Daten-Validität werden Sensitvitätstests und weitere Datenquellen herangezogen.

Ethische Aspekte. Es wird keine Intervention durchgeführt, denn die Datenerhebung beruht ausschliesslich auf einer Umfrage mittels Fragebogen. Die Auswertung der Daten erfolgt anonymisiert. Persönliche Daten und retournierte Fragebögen werden separat und unter Verschluss aufbewahrt.

Kapitel I beinhaltet Inzidenz-Raten und Risikofaktoren von Reisediarrhöe. Mittels der oben genannten Methodik konnte gezeigt werden, dass unter einer Teilnahmerate von 81.9% unter 2800 Gereisten die Befallrate von Reisedurchfall 34.4% und die mittlere 2-Wochen-Inzidenz 27.2% beträgt. Höchste Inzidenzraten sind für den indischen Subkontinent gefunden worden (35.5%) und Westafrika (45.5%). Signifikante Risikofaktoren resultierend aus einer Multivariaten Analyse ergeben sich aus einer durchgemachten Diarrhöe-Episode bis 4 Monate vor der Abreise (Risikorate RR 2.04; 95% CI 1.59-2.61), Antidepressiva als Co-Medikation (RR 2.10; 95% CI 1.16-3.78), allergischem Asthma (RR 1.67; 95%CI 1.10-2.54) und aus einer Fiebererkrankung auf Reise (RR 6.56; 95%CI 3.07-14.06), die nicht im Zusammenhang steht mit Fieber als Begleitsymptom von Reisedurchfall. Demzufolge bleibt Reisedurchfall eine der häufigsten Reiseerkrankungen.

Kapitel II umkreist die eigentliche Fragestellung, ob Reisediarrhöe zu Reizdarmsyndrom führt, beantwortet in welchem Umfang Reisende davon betroffen sind und welche Risken letztlich zu Reizdarm führen könnten. Bei einer Teilnahmerate von 79.9% sind 38 (1.5%) Personen von 2476 Gereisten an Reizdarmsyndrom erkrankt, dabei beträgt die 6-Monats-Inzidenz 1.5% (95% Konfidenzintervall 1.1-2.0), die postinfektiöse Reizdarmsyndrom 6-Monats-Inzidenz hingegen 3.0% (1.9 – 4.2 95% CI). Als potentielle Risiken, die zu diesen Langzeitfolgen führen, wurden in unserer Multivariatenanalyse unter allen möglichen erfassten Variablen primär Reisediarrhöe (3.67; 95%CI 1.82-7.61), gefolgt von einem negativen, einschneidenden Lebensereignis (RR 3.11; 95%CI 1.43-6.78) gefunden. Auch eine durchgemachte, kurze Diarrhöepisode vor Abreise (RR 2.74; 95%CI 1.43-6.78) taucht wieder als möglicher Co-Faktor, verantwortlich für die Entstehung von Reizdarmsyndrom, auf. In dieser breiten Schweizer Studienpopulation haben wir eine tiefere IBS Inzidenzrate von 1% gefunden, verglichen zu anderen Raten von Reisenden von 4-11%, sowie anderen bevölkerungsbasierten Studien mit Nicht-Reisenden. Dennoch ist IBS ein relevantes, nachhaltiges „Reiseandenken“ dessen Inzidenzrate sich der von der Grippe (Influenza) angleicht, wenngleich mit einem deutlich anderen Krankheitsverlauf. Unsere Vision wäre es, Präventionsstrategien an Risikogruppen angepasst zu entwickeln, fussend auch auf Studien mit mehr IBS Fällen für eingehendere Untergruppenanalysen.

In ***Kapitel III*** wird diese prospektiven Kohortenstudie A mit einer im Aufbau und Design ähnlichen, früheren Studie B der Forschungsgruppe des Zentrums für Reisemedizin Zürich verglichen, unter dem Aspekt der häufigsten Krankheiten oder Infekte auf Reise. Aus diesem primären Vergleich sind keine signifikanten Unterschiede zwischen den beiden Studien festgestellt worden. Zudem werden die beiden Studien mit einer retrospektiven, Schweizer GeoSentinel Studie verglichen. GeoSentinel Kliniken gehören einem globalen Netzwerk mit einer ärztebasierten Datenbankerfassung von verschiedensten Krankheitsdiagnosen. Die beiden Kohortenstudien weisen ein gemeinsames demographisches und reisecharakteristisches Muster auf. GeoSentinel Schweiz enthaltet generell kürzere Reisedauer und ein drittel der Studienpopulation sind Reisende, welche ihre Familien und Freunde in den (Sub-) Tropen besuchen (*Visiting Friends and Relatives*). Besondere Beachtung wird auch *Gender*–Unterschieden geschenkt. Eine Rangliste der häufigsten, berichteten Infektionskrankheiten von Reisenden ist erstellt worden: Diarrhöe (Befallsrate A 34.4%; B 25.9%) gefolgt von Erkältungen (A 10.2%; B 16.8%) und Fieber (A 5.3%; B 10.1%) sind die häufigsten

Beeinträchtigungen. Reisende, welche über irgendein Gesundheitsproblem auswärts berichteten, waren tendenziell jünger (RR 18-25jährige Altersgruppe der Studie A 1.53; 95%CI 1.12-2.08 und 12-25jährige Altersgruppe der Studie B 1.12; 95%CI 0.85-1.47), sie reisten länger (RR kontinuierliche Reisewochen A 1.27; 95%CI 1.20-1.36 und B 1.05; 95%CI 1.05-1.11) und sie hatten öfters den indischen Subkontinent besucht (RR A 1.79; 95%CI 1.38-2.36 und B 2.07; 95%CI 1.36-3.16). Frauen litten mehr unter Verstopfung und Insektenstichen, Männer erkrankten häufiger an Fieber. Diese Zahlen ergänzen sich zu den GeoSentinel Daten, letztere mit allerdings mehr Besucher von Freunde und Familie (VFR), welche ein anderes Risikoprofil für Infektionskrankheiten aufweisen. Interessanterweise haben wir festgestellt, dass etwa 8% (Studie A, B und andere von Hill et. al.) einen Arzt auf Reise aufsuchen, was die Interpretation erlaubt, dass reisemedizinisch beratene Touristen, Geschäftsreisende und die Besucher ihrer Familien und Freunde mit Impfstatus auf neustem Stand zum Grossteil weniger auf Arztbesuche angewiesen sind, ausser wenn Fieber oder schwere Symptome auftreten (Beispiel Malaria-Ausschluss). Diarrhöe war in jedem Studienfall häufig. In Zukunft braucht es ein genaueres Erfassen spezieller Risikogruppen und die Evaluation prophylaktischer Interventionen.

Prospektiv gesammelte Fragebogendaten haben den Vorteil, dass man vor und nach der Reise evaluiert, der Expositionsfaktor spielt die Hauptrolle, die Falldefinitionen müssen zuverlässig formuliert werden. Prospektive Studien geben eine Übersicht, man berechnet aus selbst-rapportierten Fragebögen Inzidenzen und Risikoraten aus einer Population von meist Gesunden. Retrospektives Studiendesign basiert auf meist Arztdiagnosen, die Erfassung des Expositionsfaktor kann verzerrt sein. Retrospektive Daten von Kliniken fokussieren mehr auf schlimmere oder persistierende Fälle und summieren Malaria, sexuell übertragene Krankheiten und seltene Tropenkrankheiten (*Neglected Tropical Diseases*) auf.

CHAPTER I

Diarrhoea in a Large Prospective Cohort of European Travellers to Resource-Limited Destinations

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ABSTRACT

Background. Risk factors of travellers' diarrhoea (TD) are insufficiently known, incidence rates need to be updated.

Methods. Between July 2006 and January 2008 adult customers of our Travel Health Centre leaving to a low income country for a duration of 1 to 8 weeks were invited to participate in a prospective cohort study. They received one questionnaire pre- and a second one immediately post-travel. Two-week incidence rates were calculated for TD episodes, risk assessment included demographic and travel-related variables, medical history and behavioural factors.

Results. Among the 3100 recruited, 2800 could be investigated, resulting in a participation rate of 89.2%. The TD attack rate was 34.4% (95%CI 32.6-36.1), the overall two-weeks incidence 27.2% (95%CI 26.1-28.8). The highest two-weeks incidence rates were found for West Africa (45.5%, 95%CI 37.6-53.5) and the Indian subcontinent (35.5%, 95%CI 31.2-39.8). Median TD duration was 2 days (range 1-90). The majority treated TD with loperamide (57.6%), while minorities used probiotics (23.0%) and antibiotics (6.8%). Multivariate logistic regression analysis showed that a resolved diarrhoeal episode experienced in the 4 months pre-travel (RR 2.04, 95%CI 1.59-2.61), antidepressive comedication (RR 2.10, 95%CI 1.16-3.78), allergic asthma (RR 1.67, 95%CI 1.10-2.54), and reporting TD-independent fever (RR 6.56, 95%CI 3.07-14.06) were the most prominent risk factors of TD.

Conclusions. TD remains a frequent, usually self-limited travel disease. Patients with pre-travel diarrhoea more often develop TD while abroad. Risk factors like allergic asthma in the patients' history and TD-independent fever will need further investigation.

INTRODUCTION

Travellers' diarrhoea (TD), the most common health problem in visitors to tropical and subtropical destinations, affects between 20 to over 60% of persons during a two weeks stay in a high risk country such as India or Kenya (1, 2, 14). As many of those data have been generated some decades ago, the aim of this study is to provide updated region-based TD incidences, to investigate risk factors, and to survey actual treatment options used.

METHODS

Study design. Basing on a protocol approved by the Ethical Commission of the Canton of Zurich, we have performed a prospective questionnaire-based cohort study.

Study population. Potential participants were recruited at the Centre for Travel Health of the University of Zurich between July 2006 and January 2008. To be included, participants had to be at least 18 year-old German-speaking Swiss residents who planned to travel to high-risk TD destinations (1, 15) for a duration of 1 to 8 weeks. Subjects planning to take prophylactic antibiotics during their trip, those who reported a history of severe illness (anemia, cancer, immunodeficiency or immunosuppressive disorders, severe psychiatric illness, previous gastrointestinal surgery), functional organic gastrointestinal disorders (according to Rome II (16)/ Rome III (17) criteria), recurring diarrhoeal symptoms within a four months pre-travel period, and pregnant women were excluded.

Definitions. Basing on the UNICEF/WHO definition, TD was defined as three or more unformed stools per 24 h with or without at least one accompanying symptom (nausea, vomiting, abdominal cramps, tenesmus, fever, blood in stools)(18, 19), while 3 or more unformed stools with additional symptom are named classic TD (20, 21). Patients with one or two loose stools per 24 h abroad had mild diarrhoea (19, 21). Only TD was used for incidence calculations and for multivariate analysis. Those who reported fever or blood in their TD stools were rated as dysentery. Multiple episodes of TD had to be separated by a TD-free interval of at least 72 hours. Incapacitation meant an inability to pursue planned travel activities and it was rated in 3 subgroups; severe was defined by being confined to bed for at least 12 hours or by consulting a doctor (15, 20). Body Mass Index (BMI) was calculated from participants' height and weight data at enrolment. Countries and subcontinents were grouped according to the United Nations World Migrant Stock (22). Comedication and diseases were classified by main categories of the International Classification of Diseases (ICD-10 2007)(23).

Study conduct. Participants who visited our Centre for Travel Health for standard pre-travel consultation were invited to participate in the study on a voluntary basis. Upon signing an informed consent, they received two questionnaires. Q1 was collected immediately upon completion, while Q2 was to be returned in the first week after return reminded by mail or email; Q2 was similar to a diary. During the pre-travel consultation the volunteers also obtained standard information about TD risks, options for prevention and for self-therapy, and guidance on when it is advisable to consult a physician for TD.

Q1 included 30-structured questions to assess the itinerary, previous travel to the tropics, demographic data, the body mass index, chronic diseases, confirmed allergies, and pre-travel diarrhoea characteristics. Also adverse life events in the preceding 12 months, self-reported stress, smoking habits and alcohol consumption, and perceived susceptibility to diarrhoea were investigated.

Q2 consisted of 17-questions to confirm the travel itinerary and to document a detailed history of TD abroad, including TD medication used. After an initial trial phase of three

months we added questions about syndromes abroad (also including the number of TD episodes) and about attitudes towards diarrhoea (24, 25). Non-responders were reminded by mail twice; patients reporting uncured diarrhoea were followed until resolution. Those who refused to respond to Q2 were interviewed with the single question whether they had experienced diarrhoea while abroad. No stool samples were collected in this study.

Statistical analysis. Data were analyzed using Stata statistical software, version 10.1 (Stata).

To calculate the average two-weeks incidences in various subcontinents we considered all the reported number of TD episodes reported and accounted for any two weeks of stay. The 95% confidence intervals (CI) for the incidence rates in various subcontinent were estimated as per Newcombe (26). We calculated also the first two weeks of stay testing for sensitivity.

We compared differences in proportions of demographics, attitudes and clinical variables by the chi square and Wilcoxon rank sum tests. The significance level was set at α (alpha) = 0.05. All travel- and traveller-related risk factors were evaluated as independent potential risk factors for the development of TD in a multivariate logistic regression model. Relative risks (RR) were determined by stepwise procedure. Questions inserted later (such as e.g. perceived susceptibility towards diarrhoea and tap water consumption) were analyzed by imputing missing values using gender, destination continent and education for the multivariate analysis. As sensitivity test for the multivariate analysis we compared first the complete dataset with a selection of half of the data. Second, we used the classic TD definition as outcome.

We observed the similarities and differences in reporting severe incapacitation in contrast to severe symptoms.

RESULTS

Demographics. Among 3100 enrolled travellers 2800 (90.3%) were eligible for analysis (figure 1). Gender was approximately equally distributed (Table 1). Mean age was 38.8 ± 12.6 years (median 35) and half of the population (1403, 51.1%) had a university degree, with significant higher proportions among the business travellers (p = 0.0057). Mean travel duration was 3.2 weeks with the most frequently visited destinations being Southeast (SE) Asia (636, 22.7%), followed by East Africa (522, 18.6%), the Indian subcontinent (476, 17.0%) and South America (435,15.5%). The two-weeks TD incidence for various regions is shown in figure 2 with the highest rates reported in most parts of Africa and on the Indian subcontinent. The largest group of travellers were tourists (1539; 87.9%), while 121 (10.8%) went for business. Latter had a median travel time of 2 weeks , but 90 (5.1%) visiting friends and relatives (VFR) and tourists travelled for a median duration of 3 weeks. A significantly higher proportion of businessmen visited the Indian subcontinent (44; 15.3%, p = 0.0000) and was male (69; 57.0%, p = 0.0132). Africa was the preferred continent of tourists (508, 33.1%), while VFR mainly travelled to Latin America (38; 42.2%) and Asia (22; 24.4%). A minority visited the tropics or subtropics for the first time (208, 7.5%), among whom 92 (44.2%) rated themselves as intermediate to very susceptible to diarrhoea, compared to 940 (36.7%) among experienced travellers. Post-travel questionnaires were returned within a median of 10 days (interquartile range 2-30) after returning home.

Among other diseases (596; 25.8%), common cold (277, 9.9%) and headache (106; 3.8%) were most often mentioned. Fever independent from TD was mentioned by 45 (2.5%) study participants.

Travellers' diarrhoea. The TD attack rate among the 962 patients for the varying duration of stay abroad was 34.4 % (95% CI 32.6-36.1) and the worldwide TD incidence for any two-weeks stay 27.2% (95% CI 26.1-28.8). The incidence for the first two weeks was 26.5% (95%

CI 23.7-29.2). The majority (573 (59.6%) reported a single TD episode, 248 (30.2%) suffered from more than one episode while abroad. The number of TD episodes experienced increased approximately linearly with the duration of stay as illustrated in figure 3. A total of 785 suffered of classic TD while abroad (28.0%; 95%CI 26.4-29.7) and 303 (10.8%) experienced mild diarrhoea. The most frequent accompanying symptoms were tenesmus (56.0%) and cramps (49.2%). Fever (mean 38.4 ± 0.8 °C) or vomiting accounted for about 15% each (146 with fever, 136 vomiting), and 166 (17.3%) study subjects suffered from dysentery. The three top 2 weeks incidence rates for dysentery were recorded in Middle and in Western Africa, and on the Indian subcontinent (figure 2).

All characteristics of diarrhoea of the index travel are summarised in table 3. TD patients reporting treatment with loperamide (antibiotics excluded) were found to have more TD episodes (RR 1.45, 95% CI 1.05-2.19, p=0.0026). In contrast, antibiotic or probiotic use for TD had no significant influence on the number of TD episodes reported (p=0.282, p =0.532, respectively).

TD occurred on average within 2.1 weeks after arrival (median 2 days) and patients counted on average 4 stools per day. One of nine (111, 11.5%) experienced diarrhoea for longer than one week, with 37 (3.8%) individuals suffering from persistent and 11 (1.1%) from chronic diarrhoea. Roughly two thirds of the patients (614, 65.0%) could pursue their planned activities, but 102 (10.8%) were confined to bed or consulted a physician.

Among treated patients, 343 (57.6%) chose an antimotility agent for self-medication of TD, 137 (23.0%) a probiotic and 51 combined both .116 (12.3%) TD patients reported any intake of antibiotics, 65 of them (56.0%) for diarrhoea. Most frequently used antibiotics against TD were quinolones (e.g. ciprofloxacin 25), but also trimethoprim-sulfamethoxazole (6 cases). The use of charcoal was reported by 70 persons (19.5%). Oral rehydratation therapy was mentioned in 62 (6.4%) of the TD subjects and in 16 (9.6%) of dysenteric subjects. Among the dysentery cases, 35 (21.1%) were treated with an antibiotic, 79 (47.6%) used exclusively non-antibiotic medication, mostly loperamide (n = 38). Against medical advice, 152 (58.7%; p= 0.0191) travellers with an academic background reported consumption of tap water, 60 (39.5%) of those developed TD. Health characteristics and some preventive attitudes are reported in table 2.

Factors influencing TD. Table 4 shows risk factors independently associated with TD with increasing age being the only protective one. We found significant associations neither with other reported allergies (e.g. hay fever, atopic dermatitis), nor with other pre-travel co-medications (e.g. hormonal). Seasonality was not linked to TD.

DISCUSSION

In view of the fact that TD incidence has been reduced in some countries such as Jamaica (27) and Thailand (28), updated worldwide regional incidence data were long due. For most regions they stay in the same order of magnitude (19, 29), particularly if we consider that here TD rates are presented in contrast to classic TD rates in most previous surveys (1, 2, 30). Using the classic TD definition we detected no significantly different attack rates or risk factors. Only East Asia, including China, and to a lesser degree also Latin America, showed a marked decrease. Known high-risk TD destinations such as the Middle East, North Africa and the Caribbean are in our study underrepresented, since visitors to those destinations generally do not consider a pre-travel consultation as indicated (31). Younger age and longer duration of travel are well known TD risk factors. In contrast, neither smoking, consuming alcohol nor gender influenced the occurrence of TD significantly. TD cases, who previously had

experienced TD, reported a significantly higher susceptibility to diarrhoea (p=0.0127); that may be associated with genetic factors (32, 33).

Allergic asthma, mental/behavioural co-medication, a high BMI, and a TD-independent fever episode to our knowledge have so far never been considered risk factors for TD. Such findings, however, may be clinically relevant and enhanced preventive measures to protect travellers vulnerable to multiple health impairments abroad should be considered. Allergic asthma as risk factor needs further exploration (34, 35), but in contrast, both atopy and hay fever did not influence TD in our cohort. Within psychiatric co-medication, mainly antidepressants might be associated with diarrhoea as a side-effect (36, 37), also the hypothalamic-pituary-adrenal axis might play a role (38). An elevated BMI resulted in a marginally increased risk ratio. A high BMI also is a predisposing factor for community-based diarrhoea (39-41). Obese people have a higher food intake, they may thus consume a larger inoculum of pathogens. Lastly, a fever episode independent from TD is suggestive for some low-grade inflammatory and/or immunological process (9, 42).

Loperamide was widely used to treat TD in our cohort, which is consistent with other reports (19, 43) and some of the guidelines (44, 45). Only a minority of 6.8% of all cases relied on an antibiotic for TD, which in most cases was carried in their travel medical kit. Almost 10% turned to a local pharmacy, potentially exposing themselves to the risk of fake medication abroad or inadequate storage temperatures (46, 47).

Our study design with inherent selection bias (48) and missing chronology of TD treatment does not allow an evaluation of the various treatment schedules. However, patients without antibiotic TD treatment (mostly they used loperamide) were found to have significantly more TD episodes.

Half of our study population had an university degree, travelling mostly as tourists but also for business. They might spend more money for travels and be likely to ask for pre-travel medical advice. Hence, our results, although not ideal with respect to behaviour, may reflect a rather high socio-economic stratum. As our study participants all got the usual advice on hygiene measures to prevent TD, and as many were non compliant these approaches have to be improved, or other means of prophylaxis must be used. For instance, we can increase the public and tourism industry demand to food safety to reduce the burden of TD among travellers (49).

Potential conflicts of interest. RS has accepted fees for speaking at, organizing, and chairing education, consulting, and/or advisory boards, has received reimbursement for attending meetings, and has received funds for research from Astral, Baxter, Crucell, Chiron Behring, GlaxoSmithKline, Intercell, Novartis, Salix Pharmaceuticals, Sanofi Pasteur MSD, and Santarus. All other authors report no conflict of interest.

Authors contributions. MM and RS were involved in study design and supervision. RP and MM were involved in data collection. RP, MM and RS were involved in the analysis and interpretation of the data. AT provided statistical expertise. All authors drafted the article and were responsible for critical revision for intellectual content. RP, RS, AT and MM gave final approval of the article.

Table 2. Health characteristics and TD-preventive attitudes abroad (N = 2800).

	Total[1)]	subgroups		*p* value[2)]
		TD	no diarrhoea abroad	
		n = 962	n = 1535	
Body Mass Index	n = 2789			0.3414
< 18.5	91 (3.3)	32 (35.2)	50 (54.9)	Reference
18.5-29.9	2612 (93.7)	892 (34.2)	1437 (55.0)	Reference
≥ 30.0	86 (3.0)	34 (39.5)	43 (50.0)	0.3007
Allergy (MD assessed)[3)]	n = 2785			
any	632 (34.0)	330 (52.2)	522 (82.6)	0.3297
allergic asthma	110 (17.5)	50 (45.5)	49 (44.5)	0.0124
Comedication[3)]	n = 2800			
mental / behavioural[4)]	52 (16.8)	25 (23.6)	22 (13.3)	0.0348
History of diarrhoea	n = 1843	n = 674	n = 954	
TD ever experienced	955 (51.8)	377 (39.5)	468 (49.0)	0.0295
History of TD incapacitation	n = 1029	n = 373	n = 497	
low	528 (51.3)	197 (37.3)	266 (50.4)	Reference
intermediate to severe	501 (48.7)	215 (42.9)	231 (46.1)	0.0049
Subjective diarrhoea susceptibility	n = 1656	n = 584	n = 886	
low	617 (37.3)	186 (30.1)	377 (61.1)	Reference
intermediate	974 (58.8)	363 (37.3)	486 (49.9)	Reference
high	65 (3.9)	35 (53.8)	23 (35.4)	0.0011
Diarrhoea episode	n = 2800	n = 960	n = 1535	0.0000
< 4 months before index travel[5)]	347 (12.4)	172 (49.6)	133 (38.3)	
Catering[3)]	n = 2323	n = 792	n = 1279	
Buffet meals	2190 (94.3)	742 (33.9)	1214 (55.4)	0.2346
Private / family meals	982 (42.3)	374 (38.1)	465 (47.4)	0.0027
Street vendors meals	882 (38.0)	310 (35.1)	474 (53.7)	0.3316
Adherence to *"cook it, boil it, peel it or forget it"*	n = 2318			
	1428 (61.6)	477 (33.4)	791 (55.4)	0.2996

NOTE. $p < 0.05$ was considered statistically significant. NS, not significant

[1)] Included mentioned subgroups and mild diarrhoea cases

[2)] Wilcoxon rank sum test relative to TD

[3)] Multiple answers possible

[4)] Mainly antidepressive (n=49)

[5)] Pre-existing FGID (Functional Gastrointestinal Disease) patients and subjects with diarrhoea unresolved or lasting ≥ 14d within this diarrhoea episode < 4 months before index travel were excluded as defined in exclusion criteria

Table 4. Risk factors for developing TD
in a multivariate logistic regression analysis controlled for gender (N = 2565).
Significant risk factors among all reported variables.

Variable	Risk Ratio	95% CI	*p*
Gender	0.96	0.80-1.15	0.651
TD independent fever	6.56	3.06-14.04	0.000
Psychiatric comedication	2.11	1.17-3.80	0.013
Diarrhoea pre-travel	2.03	1.59-2.54	0.000
Allergic asthma	1.67	1.10-2.54	0.018
Malaria chemoprophylaxis	1.38	1.12-1.70	0.002
Travel duration	1.28	1.21-1.35	0.000
Body Mass Index	1.04	1.01-1.08	0.004
Age	0.98	0.98-.99	0.000

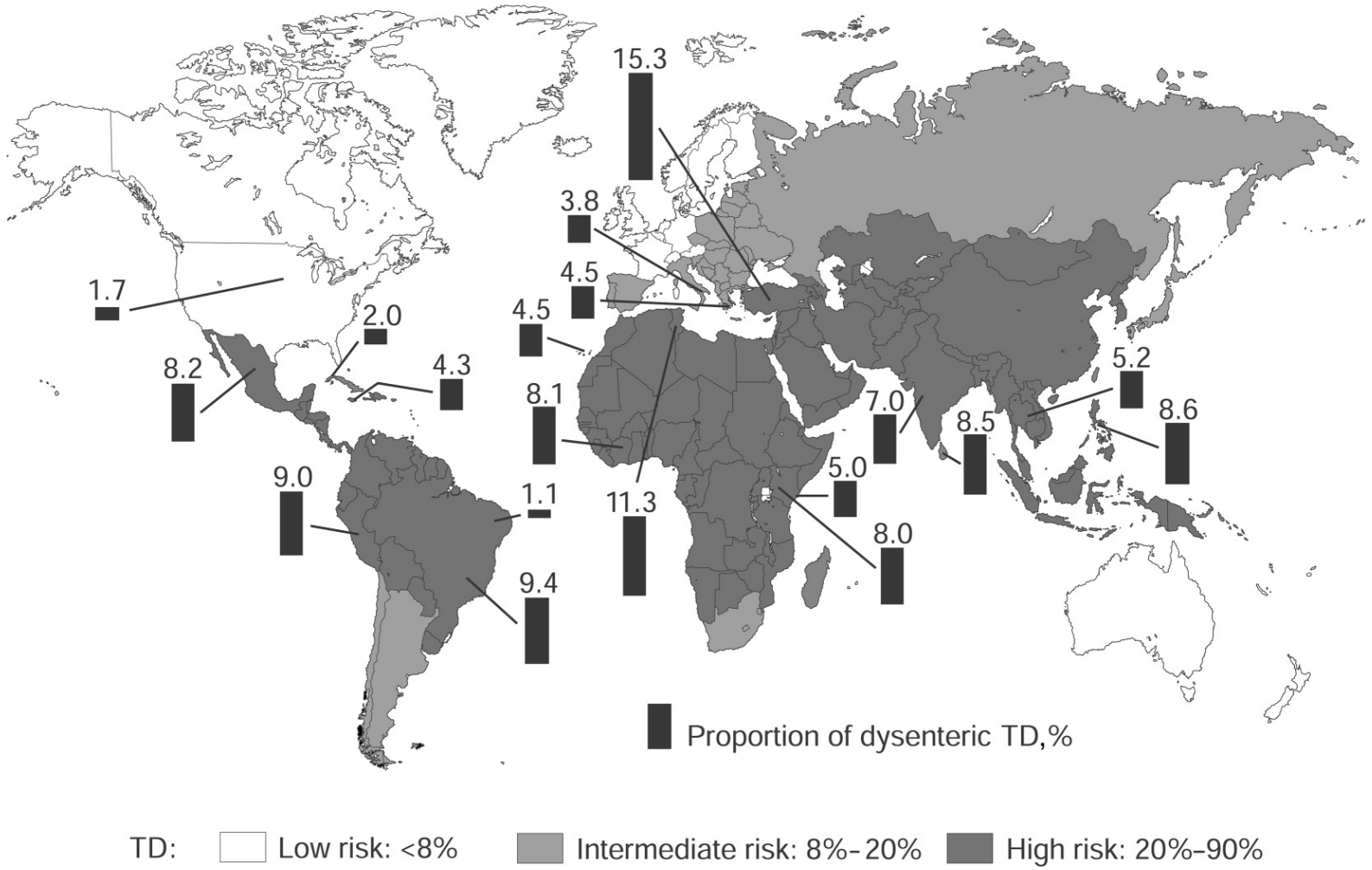
LEGENDS FOR FIGURES

Figure 1. Overview of prospective participants recruitment.
[1)] functional gastrointestinal disease
[2)] Informed consent

Figure 2. Two weeks incidences for TD and dysentery in selected areas. (N = 2794)
Blue (dark in black & white) are 2 weeks incidences for TD (n=962)
Below red (grey in black & white) are 2 weeks incidences for dysentery (n=166)
Pinned subcontinents have TD rates over 35.0 and dysentery rates over 5.0

Figure 3. Number of TD episodes by weeks of stay at a high-risk region. (n=821)
1) 1 episode (n= 573). Median 3 (1-8), mean 3.4 ± 1.7 weeks
2) 2 episodes (≥72h-interval) (n=189). Median 3.5 (1-8), mean 4.1 ± 2.0 weeks
3) 3 episodes (≥72h-interval) (n=51). Median 4 (2-8), mean 4.4 ± 2.0 weeks
4) 4 episodes (≥72h-interval) (n=8). Median 6 (2-8), mean 5.9 ± 2.0 weeks
Missing episodes n= 141 (14.7%)

Figure 1. *Risk areas for travellers' diarrhoea (2 weeks incidence rates and proportion of dysentery)* (1).



TABLES AND FIGURES

Table 1. Demographic and selected behavioural factors of the travellers' cohort (N = 2800).

	Total	subgroups			
		TD	mild diarrhoea	no diarrhoea abroad	*p* value[1)]
		n = 962	n = 303	n = 1535	
Sex	n = 2800				0.1501
Female	1406 (50.2)	466 (31.1)	151 (10.7)	789 (51.6)	
Male	1394 (49.8)	496 (35.6)	152 (10.9)	746 (53.5)	
Age group, years	n = 2672				0.0000
18-30	829 (31.0)	338 (40.8)	93 (11.2)	389 (46.9)	
31-40	882 (33.0)	283 (32.1)	102 (11.6)	497 (56.3)	
41-60	734 (27.5)	242 (33.0)	76 (10.4)	416 (56.7)	
> 60	227 (8.5)	55 (24.2)	18 (7.9)	154 (67.8)	
Origin (birth and first 5 years of life)	n = 2764				
European	2616 (94.6)	899 (34.4)	287 (11.0)	1430 (54.7)	Reference
TD risk country	148 (5.3)	49 (33.1)	14 (9.5)	85 (57.4)	0.5797
Education	n = 2745				
Vocational school level 1 [2)]	558 (21.4)	196 (35.1)	71 (12.7)	324 (58.1)	Reference
Vocational school level 2 [3)]	754 (27.5)	258 (34.2)	75 (9.9)	421 (55.8)	Reference
University	1403 (51.1)	504 (35.9)	152 (10.8)	758 (54.0)	0.3881
Destination[4)]	n = 2790				
Africa	903 (32.4)	313 (34.7)	107 (11.8)	483 (53.5)	Reference
Asia	1266 (45.4)	407 (32.1)	126 (10.0)	733 (57.9)	0.0153
Latin America	617 (22.1)	234 (37.9)	70 (11.3)	313 (50.7)	Reference

Travel type	n = 1750				
Tourism	1539 (87.9)	545 (35.4)	173 (11.2)	821 (53.3)	Reference
Family / VFR	90 (5.1)	42 (46.6)	15 (16.6)	33 (36.7)	0.0252
Business	121 (10.8)	37 (30.6)	10 (8.3)	74 (61.2)	0.2261
Travel duration, weeks	n = 2800				
mean ± sd	3.2 ± 1.6	3.6 ± 1.9	3.2 ± 1.6	3.0 ± 1.4	0.0000
median (range)	3 (1-8)	3 (1-8)	3 (1-8)	3 (1-8)	
History of travel	n = 2768				
Experienced	2560 (92.5)	867 (33.9)	275 (10.7)	1418 (55.4)	Reference
Newcomer (first such journey)	208 (7.5)	84 (40.4)	24 (11.5)	100 (48.1)	0.0388
Smoking habits	n = 2788				
previous smoker	379 (13.5)	128 (33.8)	100 (26.4)	209 (55.1)	0.6017
smoker	872 (31.2)	314 (36.0)	81 (9.3)	477 (54.7)	0.1999
Daily alcohol consumption	n = 2790				
yes	594 (21.3)	200 (33.7)	70 (11.8)	324 (54.5)	0.8816
> 1 glass daily	90 (15.4)	32 (35.6)	10 (11.1)	48 (53.3)	0.7831

NOTE. TD is travellers' diarrhoea. VFR is visiting friends and relatives.
[1)] Wilcoxon rank sum test, $p < 0.05$ was considered statistically significant referring to TD
[2)] Swiss obligatory school to apprenticeship school
[3)] Swiss *Matura* (general qualification for university access) and federal diplomas
[4)] Oceania was omitted due to only 4 travellers.

Table 3. Diarrhoea characteristics during travel (N = 2800).

	TD n = 962	mild diarrhoea n = 303	*p* value[1)]
Number of episodes	n = 821	NA [2)]	
1	573 (69.8)		
≥ 2	248 (30.2)		
Onset, weeks	n = 915	n = 267	
mean ± sd	2.1 ± 1.4	1.8 ± 1.1	
median (range)	2 (1-10)	2 (1-9)	
Unformed stools per 24h	n = 962	n = 273	
mean ± sd	5.2 ± 2.8	1.7 ± 0.4	
median (range)	4 (3-15)	2 (1-2)	
Duration, days	n = 962	n = 279	
0-3	667 (69.3)	220 (78.9)	
4-7	168 (17.5)	35 (12.5)	
8-13	63 (6.5)	13 (4.7)	
14-29 (persistent)	37 (3.8)	11 (3.9)	
≥ 30 (chronic)	11 (1.1)	0 (0.0)	
Incapacitation	n = 945	n = 292	
low	614 (65.0)	260 (89.0)	Reference
intermediate	229 (24.2)	24 (8.2)	Reference
severe	102 (10.8)	8 (2.7)	0.0000

Medication [3]	n = 957		n = 298	
any treatment against diarrhoea		596 (62.3)	144 (48.3)	
loperamide		343 (57.6)	80 (55.6)	
probiotic		137 (23.0)	27 (18.8)	
charcoal		70 (19.5)	8 (5.6)	
other		46 (7.7)	29 (20.1)	
antibiotic for TD		65 (6.8)	6 (2.0)	
antibiotic and loperamide		38 (4.0)	3 (1.0)	
antibiotic and probiotic		12 (1.2)	0 (0.0)	
oral rehydration therapy		62 (6.5)	7 (2.3)	
Measures taken against TD	n = 787		n = 207	
none		347 (44.1)	112 (54.1)	
single				
Medication from travel kit		211 (26.8)	49 (24.4)	0.2147
Medication from pharmacy abroad		77 (9.8)	10 (4.8)	0.0840
MD consultation abroad		60 (7.6)	10 (4.8)	0.0000
hospitalisation overnight		5 (0.6)	0 (0.0)	
MD at home		49 (6.2)	6 (2.9)	
other (e.g. diet, phone call to MD...)		27 (3.4)	17 (8.2)	
multiple				
travel kit + MD abroad		4 (0.5)	0 (0)	
travel kit + pharmacy abroad		3 (0.4)	3 (1.5)	
MD abroad + pharmacy		4 (0.5)	0 (0)	

NOTE. $p < 0.05$ was considered statistically significant.[1] Wilcoxon rank sum test with TD [2] NA not applied [3] multiple answers possible

Figure 1

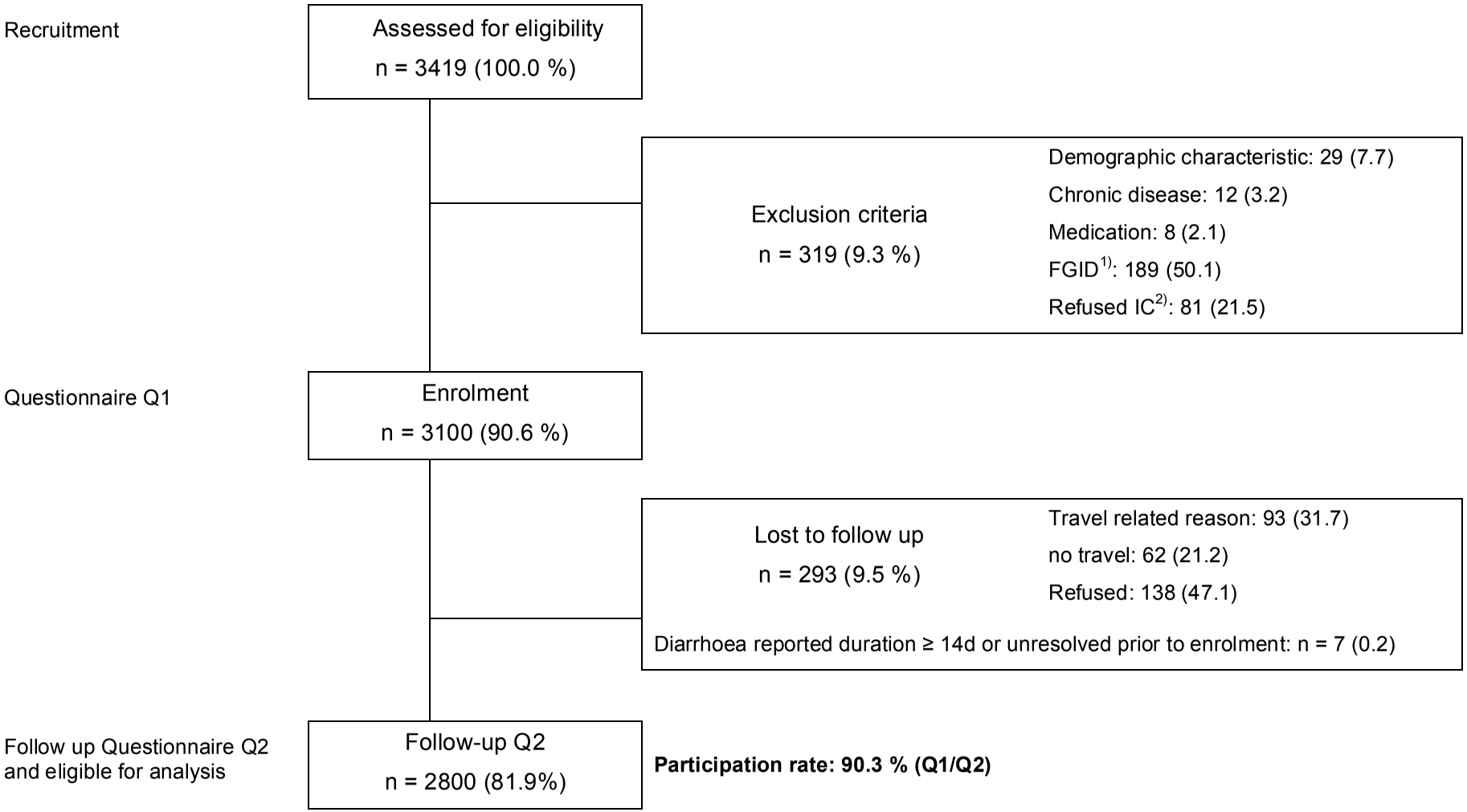

Recruitment
Assessed for eligibility
n = 3419 (100.0 %)
Exclusion criteria
n = 319 (9.3 %)
Demographic characteristic: 29 (7.7)
Chronic disease: 12 (3.2)
Medication: 8 (2.1)
FGID1): 189 (50.1)
Refused IC2): 81 (21.5)
Questionnaire Q1
Enrolment
n = 3100 (90.6 %)
Lost to follow up
n = 293 (9.5 %)
Travel related reason: 93 (31.7)
no travel: 62 (21.2)
Refused: 138 (47.1)
Diarrhoea reported duration ≥ 14d or unresolved prior to enrolment: n = 7 (0.2)
Follow up Questionnaire Q2
and eligible for analysis
Follow-up Q2
n = 2800 (81.9%)
Participation rate: 90.3 % (Q1/Q2)

Figure 2

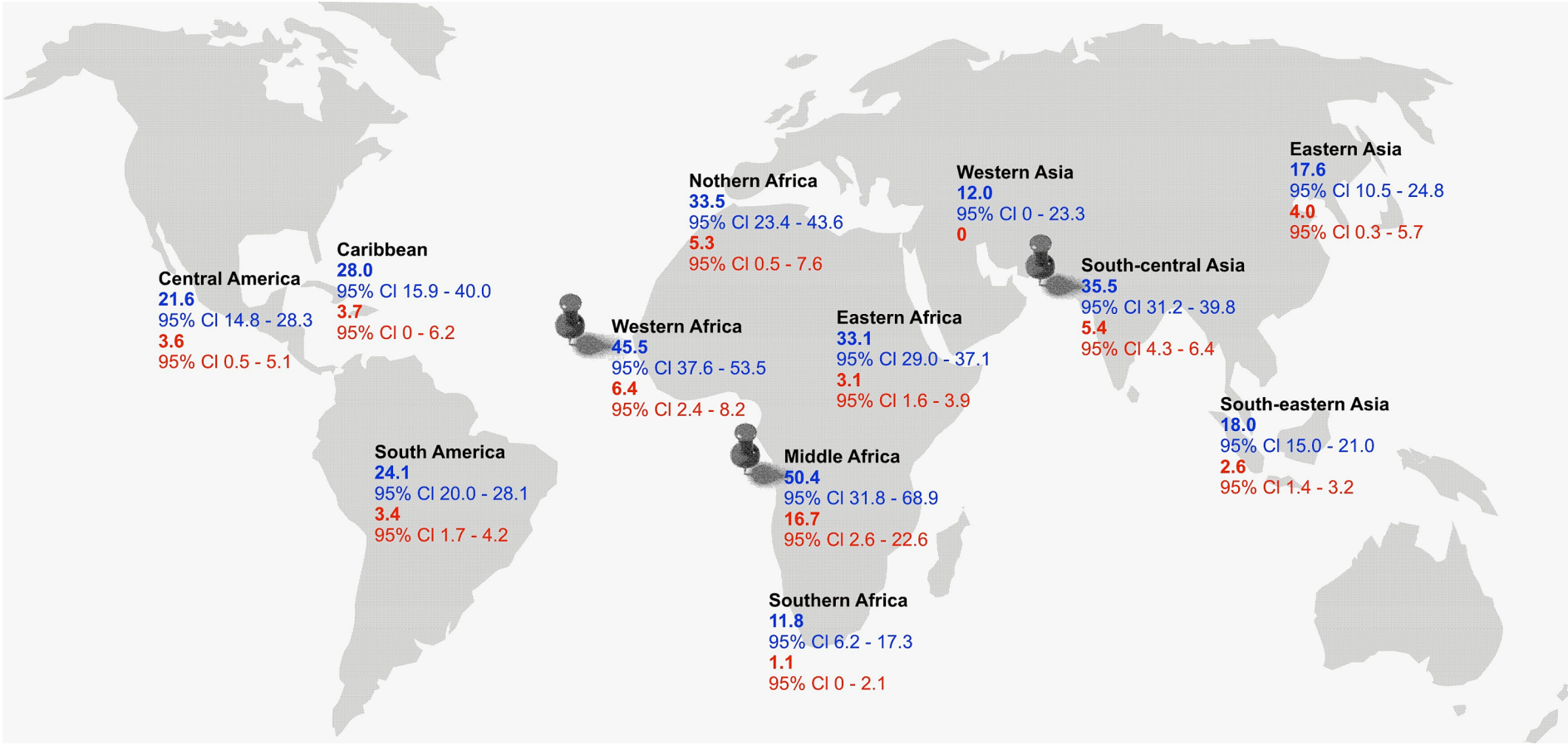
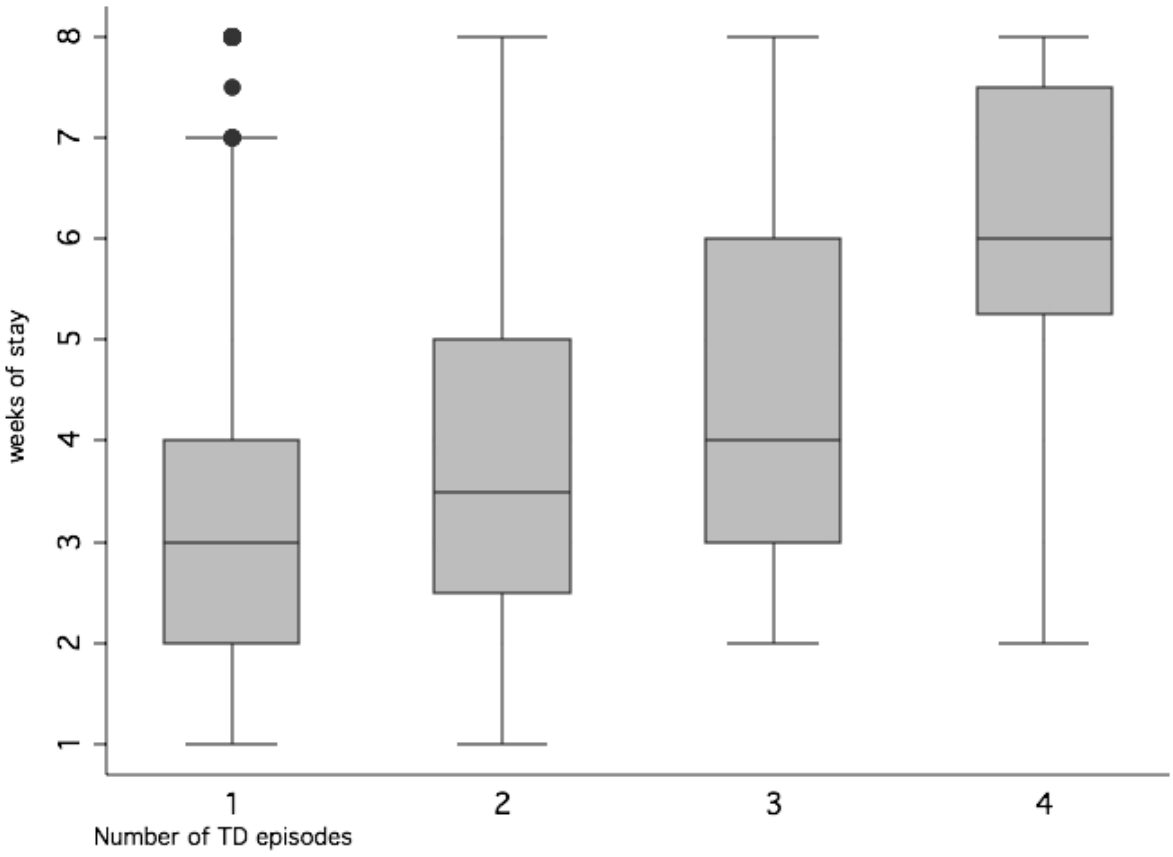

Central America
21.6
95% CI 14.8 - 28.3
3.6
95% CI 0.5 - 5.1
Caribbean
28.0
95% CI 15.9 - 40.0
3.7
95% CI 0 - 6.2
South America
24.1
95% CI 20.0 - 28.1
3.4
95% CI 1.7 - 4.2
Nothern Africa
33.5
95% CI 23.4 - 43.6
5.3
95% CI 0.5 - 7.6
Western Africa
45.5
95% CI 37.6 - 53.5
6.4
95% CI 2.4 - 8.2
Middle Africa
50.4
95% CI 31.8 - 68.9
16.7
95% CI 2.6 - 22.6
Eastern Africa
33.1
95% CI 29.0 - 37.1
3.1
95% CI 1.6 - 3.9
Southern Africa
11.8
95% CI 6.2 - 17.3
1.1
95% CI 0 - 2.1
Western Asia
12.0
95% CI 0 - 23.3
0
South-central Asia
35.5
95% CI 31.2 - 39.8
5.4
95% CI 4.3 - 6.4
Eastern Asia
17.6
95% CI 10.5 - 24.8
4.0
95% CI 0.3 - 5.7
South-eastern Asia
18.0
95% CI 15.0 - 21.0
2.6
95% CI 1.4 - 3.2

Figure 3



CHAPTER II

Irritable Bowel Syndrome among a Cohort of European Travellers to Resource-limited Destinations

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ABSTRACT

Background and aim. Travellers' diarrhoea (TD) remains the most frequent travel-associated infection. In various exposure settings between 3 and 36% of enteric infections were followed by a postinfectious irritable bowel syndrome (pIBS). Travel-related incidence rates of IBS base on small studies and its risk factors have been insufficiently evaluated.

Methods. In a prospective questionnaire-based cohort study adult travellers to resource-limited destinations were enrolled. Demographics, travel characteristics and medical history were assessed; those with functional or organic gastrointestinal disorders were excluded. Immediately after return, the volunteers completed a second questionnaire on TD, other health impairments, and on their food hygiene-related practices abroad. Six months post-travel IBS basing on Rome III criteria was assessed in a follow-up questionnaire. Risk factors were analyzed by multivariate logistic regression.

Findings. Among a total of 2476 subjects analysed (participation rate 72.4%), 38 (1.5%) newly developed IBS, and a 6-months-incidence rate for pIBS of 3.0% (95%CI 1.9-4.2) was recorded in TD patients. Significant risk factors were TD during the surveyed journey (RR 3.67; 95% 1.82-7.40), an adverse life event experienced within 12 months pre-travel (RR 3.11; 1.40-6.78), and a diarrhoeal episode experienced up to 4 months pre-travel (RR 2.74; 95%CI 1.34-5.61). The risk of acquiring IBS was up to sixfold increased following multiple diarrhoeal episodes.

Interpretation. In a large population of European travellers IBS had a lower incidence rate as compared to previous studies. Nevertheless this is a relevant long-term travel sequelae, requiring strategies targeted at risk-groups.

Funding. The study was self-funded by the Division of Communicable Diseases at the Institute of Social and Preventive Medicine of the University of Zurich.

INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by relapsing and fluctuating gastrointestinal symptoms, including abdominal pain, discomfort and changed bowel habits (50). The diagnosis bases on the exclusion of other functional or organic disorders and the Rome I, II and at last III criteria (51). The pathogenesis of IBS is multifaceted: genetic (52) epigenetic (53, 54), environmental (55), central nervous system and psychological characteristics (13, 56), e.g. coping with stress, have been postulated. A worldwide prevalence of 10 to 15% (57, 58) and an annual incidence of 0.2 to 7% (59, 60) were reported. Various studies indicated that an episode of acute gastroenteritis, such as travellers' diarrhoea, was an important risk factor for developing postinfectious IBS (pIBS) (9). In a meta analysis of eighteen studies pIBS incidence rates ranged from 4 to 32%; a pooled OR for developing pIBS 6 months post diarrhoea was 5.18 (95% CI 3.24-8.26) (7) respectively 7.3 (95% CI, 4.7-11.1) (61). Underlying host-related factors combined with a gastrointestinal infection appeared to induce persistent, low-grade mucosal inflammatory processes, which might alter the interaction between the immune and neuroenteric system and leading via persistent visceral hypersensitivity to symptomatic IBS (9, 62).

Travellers' diarrhoea (TD) is a very common infection, among those visiting resource-limited destinations it is usually self-limited (1). Estimating 80 million travellers to high risk destinations and a mean TD incidence rate for a two-weeks stay of 30% (19 to 66%), some 24 million would be affected per year (1). Previous studies among travellers found IBS incidence rates between 4 and 14% (5, 10, 63), but their conclusions were limited by the sample size of less than 500, the response rate and/or by their control for confounding factors. They were unable to generate data on age groups and travel destination. Therefore, we aimed to establish incidence rates of IBS among a cohort of mainly European travellers to various resource-limited countries and to identify risk groups among those generally healthy travellers. The study was approved by the Ethical Commission of the Canton of Zurich, Switzerland.

METHODS

A prospective questionnaire-based cohort study with a follow-up six months post-travel was designed. To achieve a precision of +/- 2% at the level of a 4% pIBS incidence rate with a confidence of 1-alpha = 95% a sample size of n = 369 is needed. Due to an estimated TD incidence rate of 20 to 40 % and withdrawal rates of 30 to 50 % an oversampling by a factor of 4 to 10 (in the worst case) has to be applied. That resulted in at least 1600 study participants to be included.

Participants. Adults seeking pre-travel medical health advice at the Centre of Travel Health of the University of Zurich between July, 2006 and January, 2008 were invited to voluntarily join the study. Upon having signed a written informed consent the following inclusion criteria were verified: German-speaking Swiss resident, duration of stay in a resource-limited destination with a high risk of TD (1) ranging from 1 to 8 weeks, also overall no longer than 12 weeks within the six months following the index travel. Pregnant women, those who planned to use antibiotics for prophylaxis abroad, including doxycycline to prevent malaria, and those with severe chronic illness (anaemia, cancer, HIV, other diseases related to immunosuppression or immunosuppressive medication), previous gastrointestinal surgery, history of functional (FGID) or organic gastrointestinal disorders, recurring diarrhoeal symptoms, diarrhoea lasting over 14 days within the four months pre-travel period, and lastly those with undiagnosed IBS fulfilling Rome III criteria prior to travel were excluded.

Following recruitment all subjects received standard pre-travel health advice including information on basic preventive measures against diarrhoea.

Definitions. IBS assessment was done according to the Rome III criteria (51); if associated to TD on the index trip it was defined as postinfectious IBS (pIBS) (64), while other IBS cases were labelled baseline IBS. Patients with IBS and those with similar symptoms were offered a free consultation at the Gastroenterology outpatient clinic of the Zurich University Hospital. The first consultation included a detailed medical history and physical examination. Depending on the discomfort, age and findings other examinations were performed afterward (blood and stool test, gastroscopy and colonoscopy with tissue biopsies, sonography, lactose breath test). TD and similarly pre-travel diarrhoea, were defined as three or more unformed stools per 24 hours with or without accompanying symptoms (18). A new TD episode had to be separated by a symptom-free interval of at least 72 hours. Continents and subcontinents were grouped according to the United Nations World Migrant Stock (22). Origin was the country in which the participant spent the first five years of life. 'Newcomers' were visiting the index travel region for the first time. The main categories of the International Classification of Diseases (ICD-10 2007) were used for co-medication and concomitant diseases. Allergies formed a separate disease entity including allergic asthma, allergic rhinitis, hymenoptera and atopic dermatitis, those were self-reported by the study participant, but an MD confirmation or corrected diagnosis was requested. Occurrence of major adverse life events (9) included death or major illness of a close family member or friend, loss of job or business failure, martial separation or divorce, major personal illness or injury experienced in the 12 months pre-travel.

Study procedure. Three questionnaires were distributed: Pre-travel Q1, including thirty items, was collected at enrolment and aimed to determine travel characteristics (duration of stay, destination, purpose), medical and socio-demographic predictors (including gender, age, education, comorbidity and medication, level of stress (four-scale-rating), adverse life events, height and weight, allergies, origin, newcomer). Also data on pre-travel diarrhoea, susceptibility to TD, and family history of IBS were collected (1). Questions regarding alcohol consumption and smoking were categorized according to the Swiss Health Surveys of the Swiss Federal Statistical Office (65). Q2, either kept as a diary abroad or completed immediately after return, confirmed travel characteristics and investigated details on TD. Three months after the launch of the study additional questions on other syndromes abroad and on preventive practices to avoid TD were included to Q2. Q3 included 15 items and was sent per electronic or post mail six months after return from index travel at study endpoint. Therein IBS criteria, diarrhoea and other gastrointestinal symptoms within the past six months, any gastrointestinal drugs used and additional travel to resource-limited destinations were to be recorded.

Non-responders were contacted twice by email and twice by post mail or telephone for Q2 and Q3. Q2-non-responders were invited to at least report whether they had experienced diarrhoea abroad. Missing Q3s were evaluated with respect to their diarrhoea rates assessed in Q1 and Q2. No stool samples were evaluated.

Statistics. Stata version 10.1 was used for descriptive, univariate and multivariate analyses. Differences between groups on categorical variables were tested by Fisher's exact test. Differences between groups on continuous variables were tested by the Wilcoxon ranksum test for independent samples with the alpha level of significance set at 0.05. The two weeks incidence rate and 95% confidence intervals (95%CI) were calculated based on Newcombe et al (26). A multivariate logistic regression model with IBS as outcome was used to establish relative risks (RR). At the beginning all variables were included, for later introduced variables (cf. study procedure Q2 section), we imputed the missing values based on gender, travel

continent and education. As sensitivity analyses, we evaluated independent risk factors for developing IBS with each half of the study participants, Further, we used another time schedule, assessing IBS 3 months instead of 6 months post travel.

Role of the funding source

The study was self-funded by the Division of Communicable Diseases at the Institute of Social and Preventive Medicine of the University of Zurich.

RESULTS

Study population

A total of 3420 subjects were recruited and 2476 responded all questionnaires, thus the participation rate was 72.4%. Those who had to be excluded mostly reported pre-existing FGID and undiagnosed IBS (Q1) or they had changed their travel plans (Q2, Q3), (Fig. 1). Questionnaires (Q2 and Q3) were returned within a median 10 days after the first reminder. Among the study population gender was homogeneously distributed and a median age was 36 years (range 18 – 82) (Table 1). The majority, 2320 (95.0%), originated from Europe, while 65 (2.7%), including 11 visiting friends or relatives (VFR) were from a resource-limited country. The educational level was high, 1244 (51.3%) were university graduates. Popular tourist destinations were Southeast Asia, South Asia and East Africa, the median duration of stay was 3 weeks (range 1 – 12). For 181 (7.4 %) newcomers it was their first trip to a resource-limited destination. Business travellers were predominantly male (p = 0.0087), whereas age did not correlate with the type of travel. Among the 550 (22.2%) subjects reporting confirmed allergies, hay fever (378, 69.0%) and allergic asthma (92, 16.9%) were reported most frequently. A total of 852 (34.4%) subjects suffered from TD abroad, but only 33 (3.9%) were among those 921 (62.7%) who rated themselves as being susceptible for diarrhoea. The TD incidence rate was not influenced by gender, but it occurred significantly more often in subjects under 25 years of age (p=0.0001). Males suffered significantly more often from pre-travel diarrhoea (p=0.021), while females reported more pre-travel adverse life events (p=0.008) and more susceptibility to diarrhoea (p=0.0224).

Among the 313 non-responders of Q2 and Q3, but with available diarrhoea data, 18.4% (95%CI 14.8-21.1) had experienced TD and 14.5% (95%CI 11.6-17.3) pre-travel diarrhoea.

IBS incidence rates and risk factors

Thirty-eight (1.5% of the study population) developed IBS based on Q3 data, 26 (3.0% of the TD patients) being travel-related pIBS (table 2). Considering the baseline IBS incidence rate of 0.7%, the TD attributable risk difference is 2.3%. The overall IBS incidence rate for any two-weeks of stay was 1.0% (95%CI 0.6-1.4), and 2.8% (95%CI 1.7-3.9) for the subgroup of travel-related pIBS, respectively. In the multivariate logistic regression analysis TD was the strongest independent risk factor for developing IBS; also an adverse life event, and a pre-travel diarrhoeal episode were relevant risk factors (table 3).

IBS patients more frequently reported multiple TD episodes abroad and a more severe TD course, e.g. dysenteric symptoms, than other diarrhoeal patients. For baseline IBS pre-travel diarrhoea was the only significant risk factor in the multivariate analysis (RR 3.80; 95%CI 1.12-12.79). Any diarrhoeal episode increased the risk of developing IBS more than fivefold (pre-travel diarrhoea or TD: RR 5.60; 95%CI 2.55-12.29) with insignificant differences when comparing pre-travel diarrhoea and TD. Experiencing multiple diarrhoeal attacks raised the IBS risk by sixfold (RR 6.01; 95%CI 2.02-17.89) when controlled for gender, age and an adverse life event. For all the above analyses a concordant about threefold increased risk for having experienced an adverse life event within the past 12 months was detected.

For the sensitivity analysis the multivariate logistic regression results of the total study population were compared to the ones of each half and the same independent risk factors were found. For a follow-up period limited to 3 months post-travel a lower overall 3-months-IBS incidence rate (0.9%; 95%CI 0.5-1.3; n=22) was detected and the corresponding overall travel-duration-related IBS incidence for any two-weeks of stay was 0.6% (95%CI 0.3 -0.9).

IBS classification and healthcare utilization

The majority of IBS patients were classified as mixed IBS-M (31, 81.6%), four patients (10.5%) had diarrhoea-predominant IBS-D, three (7.9%) constipation-predominant IBS-C. Seventeen (44%) patients sought medical care, ten among them spontaneously consulted a physician and the remaining seven were supposed to visit the Gastroenterology outpatient clinic at the University Hospital. Three of them were diagnosed with IBS, one patient was diagnosed with lactose intolerance, blastocystis hominis was found in one patient, one had a prolonged travellers diarrhea and the seventh patient finally did not show up. Among those consulting a physician spontaneously we received one IBS-confirmation by a gastroenterologist and a self-reported case by a patient who visited several physicians. The remaining did not report results.

DISCUSSION

This is the first large prospective cohort study to focus on irritable bowel syndrome among travellers to resource-limited destinations on various continents using the Rome III criteria. New onset of IBS assessed 6 months post travel has occurred overall in 1.5%, and 3.0% had TD-related pIBS. Our IBS incidence rates are in the same range as the ones found for the general population of 1 to 3% per year, but below the pIBS rates of 3.7 to 36% (7, 61) or of the 4-14% reported for TD-related pIBS (5, 10, 63). The TD attributable risk difference of 2.3% is similar to the one of the initial Ilnickyj study reporting a risk difference of 2.6% (63), but we assessed baseline and pIBS with a far larger sample size. Our lower IBS rates in travellers may be explained by the efforts in separating diarrhoeal episodes and by the more stringent exclusion criteria; having for instance detected 189 cases of pre-existing (un-)diagnosed organic or FGID at recruitment. In addition, the destinations and the study populations differed, e.g. we included also senior citizens as compared to some of the previous studies (19). The follow-up in all previous travelers-based studies was 3 or 6 months, but diagnostic criteria used were Rome I (3 months follow-up) and Rome II (12 months). After 3 months our overall IBS-3-months incidence rate resulted the half (0.9%). Compared to the results of a meta analysis it remains uncertain whether a longer follow-up of our patients would have resulted in higher incidence rates of IBS (7).

Three kinds of selection bias might limit our study: Travellers consulting for pre-travel health advice might be either somewhat hypochondriac or represent a particularly health literate subpopulation with a positive health awareness, as 51.3% of our customers reported a university degree. The latter would result in an underestimation of the IBS risk when compared to travellers with a different educational background whereas for the former higher TD rates and also a higher rate of IBS would be expected. Actually, we found higher TD rates when compared to non-responders and this might indicate even an overestimation of our IBS incidence rate. Third, some popular tourist destinations, such as Turkey, North Africa and the Caribbean, although attracting millions of visitors, are underrepresented as those rarely consult for pre-travel health advice (66).

Diarrhoea is an important risk factor for IBS whether it occurred at home or abroad. There is evidence that new onset of IBS may be triggered by an infectious agent, but it remains unknown, whether the type of pathogen, the size of the inoculum, and the time interval between diarrhoeal attacks play a role (67). Of note, it appears that multiple diarrhoeal episodes would raise the IBS risk. That might support the hypothesis of IBS being a persistent or re-activated mucosal low-grade inflammation (62). As the results of the sensitivity analyses validate our risk estimates, more detailed subgroup analyses were not feasible, but such would be needed to assess factors and syndromes associated with other low-grade inflammatory processes, as e.g. bronchial hyper-responsiveness (68) or antibiotic treatment (9) were shown to be associated with IBS.

The reported threefold IBS risk following the experience of a recent adverse life event corresponds to the relative risk of 2.0 for IBS found by Gwee et al. (69) who evaluated the risk levels of psychological factors and gut dysfunction among IBS patients. In our cohort only one IBS case reported regular antidepressive medication. Contrary to some reports, female gender was not found to be a significant independent risk factor for IBS, potentially masked by underlying factors, such as mental health issues or TD characteristics.

Of practical importance for travel medicine, we estimated a TD-associated IBS risk of 2% in the 6 months following any two-weeks stay at a resource-limited destination. Still substantial and almost twice the incidence rate of self-limited influenza in a comparable population, IBS has a greater impact because it represents a long-term travel sequelae in a previously healthy population.

Research is needed to determine whether extensive preventive measures, e.g. by antibiotic prophylaxis, would reduce the risk of IBS in travellers as has been postulated (70). If this is confirmed, travel health counsellors in the pre-travel consultation could investigate predisposing factors, such as recent diarrhoeal episodes, the experience of recent adverse life events and discuss the means to reduce the risk for IBS. Further investigations also need to focus on the patho-physiological interaction of IBS predisposing factors.

Partly presented in part at the 11th Conference of the International Society of Travel Medicine, Budapest, 24–28 May 2009 (abstract FC 03.01).

Table 1: Selected sociodemographic, travel and health-related data of all travellers and those with new onset of IBS (IBS+). (Full table as online only material)

Variable		All (N=2476)	IBS + (n= 38)	p^1
Female gender		1258 (50.8)	18 (47.4)	0.669
Age, median (range) in years		n = 2370	n = 35	
		36 (18-82)	30 (19-70)	0.020
Continent visited:	Africa	808 (32.6)	14 (36.8)	0.322
	Asia	1105 (44.6)	18 (47.4)	
	Latin America	557 (22.5)	6 (15.8)	Reference
Duration of trip, median (range) in weeks		3 (1-12)	3 (1-8)	0.192
Purpose of travel		n= 2386	n= 36	
	tourism	2092 (84.5)	30 (78.9)	Reference
	visiting friends and relatives	130 (5.3)	1 (2.6)	
	business	163 (6.6)	5 (13.2)	0.091
Newcomer (first visit to resource-limited countries)		181 (7.4)	6 (15.8)	0.046
Travellers' diarrhoea (TD)		852 (34.4)	26 (68.4)	0.000
≥ 2 TD episodes		226 (9.2)	12 (31.6)	0.011
severe TD symptoms:	dysentery	146 (5.9)	8 (21.0)	0.000
	vomiting and cramps	66 (2.7)	2 (5.3)	0.445
TD duration, median (range) in days		2 (1-90)	3 (1-20)	0.312
Allergies, self reported as MD diagnosis		550 (22.2)	11 (28.9)	0.840
Hay fever		378 (15.3)	9 (23.7)	0.357
Allergic asthma		92 (3.7)	4 (10.5)	0.027
Diarrhoea ≤ 4 months pre-travel, resolved pre-departure		305 (12.3)	12 (31.6)	0.000
Duration of diarrhoea pre-travel, median (range) in days		2 (1-10)	2 (1-5)	0.988
Adverse Life Event ≤ 12 months pre-travel		n = 2452	n = 38	
		230 (9.4)	9 (23.7)	0.002
Susceptibility towards diarrhoea in general		n = 1470	n = 22	
low		549 (37.3)	4 (18.2)	Reference
intermediate		863 (58.7)	15 (6.2)	
high		58 (3.9)	3 (8.0)	0.003
Close family member with IBS		n = 1331	n = 18	
		58 (7.5)	2 (11.1)	0.158

[1)] Chi square / Wilcoxon rank sum test

Table 2: Incidence rates for irritable bowel syndrome (N = 2476)

	6-months incidence rate	**95%CI**
IBS overall	1.5 (38/2476)	1.1 – 2.0
Postinfectious IBS	3.0 (26/852)	1.9 – 4.2
Baseline IBS	0.7 (12/1624)	0.3 – 1.2

	Travel duration-related 6-months incidence for any two-weeks of stay	**95%CI**
IBS overall	1.0	0.6 – 1.4
Postinfectious IBS	2.8	1.7 – 3.9
Baseline IBS	0.9	0.5 – 1.4

Table 3: Relative risk estimation of developing IBS 6 months post-travel.

Variable	Univariate Risk ratio (95% CI) N = 2476	Multivariate regression Risk ratio (95% CI) N = 2424	Multivariate regression Risk ratio (95% CI) Base Model, N=2424
Female gender	0.87 (0.46-1.65)	0.89 (0.46-1.71)	0.89 (0.46-1.71)
Age ≤ 30 years [1)]	2.48 (1.27-4.84)	0.89 (0.76-1.04)	0.89 (0.76-1.04)
Newcomer [2)]	2.39 (0.99-5.80)	2.43 (0.98-6.02)	2.43 (0.98-1.71)
Travel duration ≥ 2 weeks	1.18 (0.98-1.41)	1.09 (0.91-1.31)	
Travel destination			
Africa vs. Asia	1.06 (0.53-2.15)	1.05 (0.52-2.15)	
Asia vs. Latin America	1.52 (0.60-3.85)	1.87 (0.71-4.90)	
Indian subcontinent vs. others	0.74 (0.29-1.91)	0.61 (0.24-1.61)	
Travel purpose			
Visiting Friends and Relatives vs. tourism	0.53 (0.72-3.94)	0.50 (0.07-3.68)	
Business vs. tourism	2.18 (0.83-5.69)	2.22 (0.83-5.92)	
Smoking	1.71 (0.90-3.29)	1.66 (0.85-3.20)	
Allergic asthma	3.18 (1.08-9.41)	2.32 (0.75-7.16)	
Adverse Life Event [3)]	3.08 (1.44-6.59)	3.11 (1.40-6.78)	3.11 (1.43-6.78)
High stress-level pre-travel	1.00 (0.30-3.28)	0.73 (0.21-2.51)	
Diarrhoea pre-travel [4)]	3.38 (1.69-6.77)	2.74 (1.34-5.61)	2.74 (1.34 – 5.61)
Travellers' diarrhoea (TD)	4.23 (2.12-8.42)	3.67 (1.82-7.40)	3.67 (1.82-7.61)
≥ 2 TD episodes	2.88 (1.22-6.76)	2.71 (1.14-6.47)	
dysentery	4.44 (2.00-9.88)	3.48 (1.53-7.93)	
Duration of TD	1.02 (0.98-1.06)	1.02 (0.97-1.06)	
Antibiotic intake on travel[5)]	2.65 (1.09-6.45)	2.27 (0.92-5.60)	
Malaria chemoprophylaxis	0.91 (0.40-2.09)	0.88 (0.38-2.03)	
TD-risk practices abroad [6)]	1.53 (0.34-6.94)	1.79 (0.39-8.29)	

Multivariate analysis controlled for gender, TD, diarrhoea pre-travel, adverse life event and newcomer (Base Model)

[1)] Age substituted by newcomer in multivariate analysis, as newcomer is dependent from age (p= 0.000)

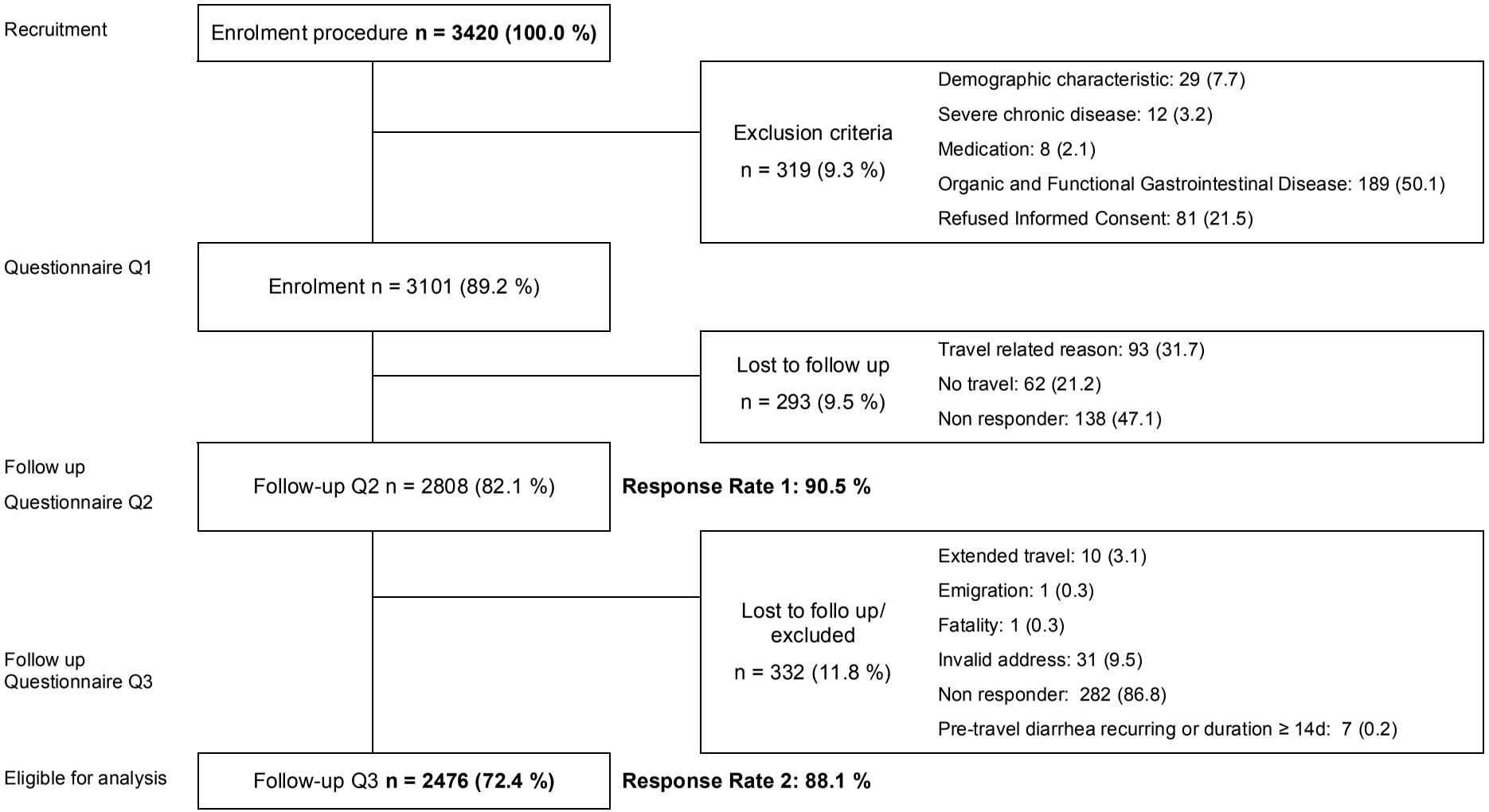
[2)] First visit to resource-limited countries

[3)] Experienced within 12 months pre-travel

[4)] Episode within 4 months pre-travel and resolved pre-travel

[5)] Subjects taking antibiotic prophylaxis excluded[6)] Self-reported non-adherence to the adage "cook it, boil it, peel it or forget it" or consuming tap water abroad

Figure 1: Flow diagram



Annex Table 1. Demographic and travel characteristics (Q1 Data). NS is not significant.

	all		IBS subgroup		*p*	pIBS subgroup		*p* pIBS vs.healt
	n = 2476	%	n = 38	%		n = 26	%	
Sex	n = 2476		n = 38			n = 26		
Female	1258	50.8	20	52.6	0.6692	12	46.2	0.6358
Male	1218	49.2	18	47.4	Reference	14	53.9	Reference
Age group, years	n = 2368		n =35		**0.0203**	n =20		**0.0317**
18-30	715	30.2	18	51.4		12	50.0	
31-40	778	32.8	7	20.0		6	25.0	
41-60	665	28.1	8	22.9		5	20.8	
> 60	210	8.8	2	5.7		1	4.2	
mean	39.1			35.0		34.4		
median	36			30		32		
stdev	12.7			12.7		12.4		
range	18-82			19-70		19-70		
Origin	n = 2442		n = 38			n = 26		
European	2320	95.0	36	94.7	EU NS CH NS	25	88.5	Reference
high TD risk country	65	2.7	1	2.6	0.9907	0	0.0	0.4024
low to interm. TD risk country	57	2.3	1	2.6	NS	1	3.9	Reference
no risk	2340	95.8	36	94.7	Reference	25	95.2	Reference
risk country	102	4.2	2	5.3	0.7359	1	3.9	0.9426
Education	n = 2427		n = 37			n = 26		
Vocational school level 1	510	21.0	8	21.6	0.6859	5	19.2	0.4372
Vocational school level 2	673	27.7	6	16.2	0.1013	3	11.5	**0.0447**
University	1244	51.3	23	62.2	Reference	18	69.2	Reference
Destinations	n = 2470		n = 38			n = 26		
Africa	808	32.7	14	36.8	0.5846	9	36.6	0.8314
Asia	1105	44.7	18	47.4	0.7424	13	50.0	0.5906
Latin Amerca	557	22.6	6	15.8	0.3150	4	15.4	0.3794
Travel type	n = 2385		n = 36			n = 25		
Tourism	2092	87.7	30	83.3	Reference	20	80.0	Reference
Family / VFR	130	5.5	1	2.8	0.5310	0	0.0	0.2630
Business	163	6.8	5	13.9	0.1040	5	20.0	**0.0138**
Travels duration, weeks			n = 38		0.1921	n = 26		**0.0366**
mean ± sd	3.4 ± 1.8		3.7± 1.9			4.1 ± 2.2		
median (range)	3 (1-12)		3 (1-8)			3.5 (2-8)		
History of travel	n = 2447		n = 38			n = 26		
Experienced	2266	92.6	32	84.2	Reference	22	84.7	Reference
Newcomer (first such journey)	181	7.4	6	15.8	**0.0464**	4	15.4	0.1131
Smoking habits	n = 2470		n = 38			n = 26		
do smoke	740	30.0	16	42.1	0.0996	12	46.2	0.0695
previous smoker	900	36.5	16	42.1	0.4705	10	38.5	0.8306
occasional smoker	405	55.1	8	21.1		7	23.1	
regular smoker	330	44.9	8	21.1	0.1581	5	19.2	0.3633
Alcohol drinking	n = 2468		n = 37			n = 25		
Daily alcohol consumption	531	21.5	8	21.6	0.9874	6	24.0	0.7647
> 1 glass daily	79	3.2	3	8.1	0.0964	1	4.0	0.8337

Annex Table 2. Health characteristics and TD exposure related factors (Q1, Q2, Q3 data).

	all		IBS subgroup		p value	pIBS subgroup (cTD =1)		p (pibs vs. Healthy)
Body Mass Index	n = 2465		n = 38		0.5329	n = 26		0.6824
< 18.5	78	3.2	1	2.6		1	3.9	
18.5-29.9	2307	93.6	26	68.4		17	65.4	
≥ 30.0	80	3.3	11	29.0		8	30.8	
mean	23		23.0			23		
median (range)	22.6 (16.1-43.4)		22.9 (18.4-29)			23.1 (18.4-27.5)		
stdev	3.2		3.0			3		
Allergy (MD confirmation reported)	550	22.3	11	28.9	0.8400	9	34.6	0.8549
hay fever	378	68.7	9	81.8	0.3570	7	31.8	0.5687
allergic asthma	92	16.7	4	36.4	**0.0271**	4	18.2	0.0023
atopic dermatitis	51	9.3	0	0.0		0	0.0	
hymenoptera	53	9.6	1	9.1		1	4.5	
other	131	23.8	2	18.2		2	9.1	
Comedication	n = 2471							
any	287	11.6	5	13.2	0.4183	3	11.5	0.995
gynecological	79	27.8	1	3.1		1	4.5	
circulatory	56	19.7	1	3.1		0	0.0	
mental / behavioral	47	16.5	1	33.3	0.7219	1	4.5	0.4552
other	102	35.9	2	66.7		1	4.5	
Medication abroad	n = 2413		n = 37			n = 25		
any	1032	42.8	18	48.6	0.4664	13	61.9	0.3477
malaria prophylaxis	491	47.6	7	38.9	0.8326	3	12.0	0.3043
antibiotic therapy	169	6.9	6	33.3	**0.0253**	6	24.0	**0.0007**
Travel illness	n = 2047		n = 29			n = 16		
any	534	26.1	12	41.4	0.0590	10	52.6	**0.0082**
fever	183	34.3	6	50.0	**0.0462**	5	62.5	**0.0198**
TD independent fever	38	0.0	0	0.0		0	0.0	
cold	197	56.8	5	41.7		4	37.5	
constipation	32	6.0	2	16.7	0.2201	2	12.5	0.0671
Stress perceived pre-travel	n = 2457		n = 38			n = 22		
none	428	17.4	6	15.8	Reference	4	18.2	Referent
low to moderate	1835	74.7	29	78.3		16	72.7	
high	194	7.9	3	7.9	0.3641	2	9.1	0.1305
Adv. life event exp. 12 months pre-travel	230	9.4	9	25.0	**0.0023**	6	23.1	**0.0144**
fatality	99	43.8	5	55.6		3	11.5	
job-loss	25	11.1	2	22.2		2	7.7	
other	106	46.1	2	22.2		1	3.8	
History of TD	n = 1630		n = 26			n = 17		
TD ever experienced	851	52.2	14	53.8	0.9030	9	47.1	0.8611
don't remember	30	1.8	0	0.0		0	0.0	
History of TD incapacitation	n = 910		n = 16			n = 10		
low	464	51.0	5	31.3	Referent	3	30.0	Referent
intermediate to severe	446	49.0	11	68.8	0.0772	7	60.0	0.2277

Diarrhoea susceptibility (self-rated)	n = 1470		n = 22			n = 15		
low	549	37.4	4	18.2	Referent	3	20.0	Referent
intermediate	863	58.7	15	68.2	0.1086	9	60.0	0.3145
high	58	4.0	3	13.6	**0.0026**	3	20.0	**0.0007**
Diarrhoea episode <4 months pre-travel	305	12.3	12	31.6	**0.0003**	8	30.8	0.0037
duration of this episode (days) mean	1.8 ± 1.5		1.8 ± 1.2		0.9878	2 ± 1.4		0.5737
median (range)	2 (1-10)		2 (1-5)			2 (1-5)		
D-episode within the 6 m post-travel	n = 2472		n = 38			n = 26		
	302	12.2	23	60.5	0.0000	16	61.5	0.0000
duration of this episode (days)					0.1081			0.1041
mean ± stdev	6.2 ± 12.2		4.8 ± 3.1			4.8 ± 3.1		
median (range)	2 (1-120)		4 (2-10)			5 (7-10)		
Ever abdominal pain pre-travel	n = 2476		n = 32			n = 26		
	15	0.6	0			0	0.0	
Family history with IBS pre-travel	58	4.4	2	16.7	**0.0360**	0	0.0	
Attitudes abroad								
Colonial rule	n = 2057		n = 31			n =22		
considered	1265	61.5	12	54.8	**0.0049**	8	36.4	**0.0092**
rule unknown	47	2.3	0	0.0		0	0.0	
Tap water consumption	224	10.9	2	6.5	0.5974	0	0.0	
Catering abroad	n = 2061		n = 31			n = 22		
Buffet meals	1945	94.4	28	90.3	0.3171	20	90.9	0.4615
Private / family meals	867	42.1	13	50.0	0.9881	9	40.9	0.9234
Street vendors meals	779	37.8	14	53.8	0.3968	12	54.5	0.1046

CHAPTER III

Evaluation of selected health problems abroad: prospective and retrospective risk assessment

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ABSTRACT

Background. Within the past decades many studies investigated travellers' health either prospectively or retrospectively. Aim is to evaluate strengths, limitations and common issues of prospective and retrospective traveller-based datasets with respect to selected common health impairments among Swiss travellers to resource-limited destinations.

Method. Two prospective questionnaire-based cohorts A (2006-08) and B (1998-2000) included adults with standard pre-travel medical advice travelling ≤ 8 weeks to resource-limited destinations. They were compared to a retrospective, post-travel and physician–based collective of Swiss patients with or without pre-travel health advice, the Swiss GeoSentinel database (2004-2005).

Results. In both cohorts travellers suffering from health problems abroad tended to be younger (RR age A(18-25 years) 1.53; 95%CI 1.12-2.08 and B (12-25 years) 1.12; 95%CI 0.85-1.47), stayed longer abroad (RR weeks of stay A 1.27; 95%CI 1.20-1.36 and B 1.08 95%CI 1.05-1.11) and had more frequently visited the Indian subcontinent (RR A 1.79; 95%CI 1.38-2.36 and B 2.07; 95%CI 1.36-3.16). Travellers of median age 36 and 31 reported any illness abroad in 43% and 40% of all 2476 (cohort A) and 1435 participants (cohort B), respectively. Diarrhoeal, attack rates (A. 34% and B: 26%) accounted for the most frequent contracted infectious impairment abroad, followed by cold (A 10%; B17%) and 5%A; 10%B participants measured fever. Physician visits for any reported illness abroad accounted for 8% for both cohorts. Females were significantly more frequently affected by constipation and insect biting, males by fever.

Conclusions. Prospectively collected questionnaire results and retrospectively assessed MD diagnosis-based data complement each other. Whereas the first provides an overview of health impairments occurring among travellers and estimates absolute risks, as e.g. incidences, the latter focus on more serious or persistent health problems needing health care utilization.

BACKGROUND

Among the various studies assessing health risks of travellers to resource-limited destinations two different main approaches might be distinguished: first, a crosssectional, usually patient-based design, such as the GeoSentinel database which collects travel characteristics retrospectively (71). Second, a prospective cohort design assessing travel- and health-related information pre-travel and including a diary to record health impairment while abroad or shortly after return (72). We aimed to contrast these two approaches to point out their strengths, limitations and common issues. Thereby, we based on known frequent health problems abroad, such as travellers' diarrhoea (TD) which affects 20-60% of individuals from industrialized countries visiting a resource-limited destination(1, 73), Pitzurra R et. al. BMC Infect Dis submitted), respiratory tract infections being with 26%(74) the second most common cause of illness in returned travellers including fever, which is as frequent as 13%(75), skin rashes abroad accounting for 8%(76) and the often neglected constipation with a suggested frequency of about 9%(77).

METHODS

Setting and participants

The two prospective travellers-based cohorts, A and B (BMC Infect Dis submitted and Isefit (72) were done in Zurich at the Travel Health Centre of the University of Zurich, and the patient-based GeoSentinel networks' dataset included data of Switzerland(78) to get a comparable study population with respect to place of residence. Cohort A was performed from July 2006 to January 2008, cohort B between January 1998 to March 2000 and Swiss included data from 2004 to 2005. Participants of cohorts A and B had all provided written informed consent and had received standard pre-travel medical advice and the standard as well as the recommended immunisations against vaccine-preventable diseases. Within GeoSentinel data information about medical pre-travel consultation and updated vaccination status was available. For reasons of comparability and of frequent occurrence diarrhoea, fever, cold symptoms and skin rashes were selected as model illness entities.

Table 1 reports an overview of case series and cohort design.

Data analysis

For the cohort studies, statistical significance of variables was assessed ranksum-Wilcoxon nonparametric tests and relative risks with 95% confidence intervals with a level of significance set at 0.05. Multivariate analysis with logistic regression was performed with adjustment for gender, age, destination, travel duration, purpose of travel and the diseases (travellers' diarrhoea, cold, fever, constipation and skin rashes) using either any disease, TD or cold as separate outcomes. Data were analyzed with the software Stata Statistics 10.1. The Swiss GeoSentinel data were based on published data and personal communication of the Swiss coordinator.

RESULTS

Demographics

Gender and age were similarly distributed among all three datasets (Table 1). Among resource-limited destinations places in Asia were most frequently visited followed by Africa and Latin America.The median travel duration was with 3 weeks slightly longer than for the GeoSentinal data with a median of 14 days. The great majority (> 80%) traveled as tourists followed by less than 10% of business travellers and VFRs (those visiting friends and relatives) whereas the VFRs accounted for more than one third in the GeoSentinel study.

Ranking of illness

Cohorts A and B did not different significantly within the symptom spectrum reported. More than half of all cohort study participants reported any health impairment (Table 2). Within the cohort studies gastrointestinal illness was most frequently mentioned followed by respiratory symptoms, common cold, fever and skin rash whereas within the Swiss GeoSentinel data gastrointestinal diseases and fever ranked at the top followed by respiratory illness and skin disorders. Of note, a total of 1045 (72.8%) reported insect bites, of which 50 (80.7%) in combination with skin rashes, but no significant association was found neither with skin rashes (p= 0.1245) nor fever (p=0.7714).

Risk factors

Figure 1 shows shows the relative risks for developing any self-reported illness abroad, including the significant RR for visiting the Indian subcontinent, longer travel durations, age below 25 in both cohorts and VFR only for cohort A.

Focusing on gender differences (for females) we found constipation to be the most prominent risk factor (RR Cohort A 2.53; 95% CI 1.14-4.53; RR Cohort B 1.71; 95% CI 1.03-2.81). The cohort A women appeared to be less at risk of experiencing fever (RR 0.74; 95% CI 0.54-1.00). Especially in relation with TD, RR for dysentery was 0.68 (95% CI 0.48-0.95). Remarkably, significantly more women reported adhering to the adage “cook it, boil it, peel it or forget it” ($p_{\text{Cohort A}}$=0.0274). More men reported tap water consumption (52.7%; p_{CohortA} = 0.224). In both cohort studies measured fever temperature was similarly distributed (median 38.5; $\text{range}_{\text{Cotravibs}}$ 37.5-41.5, $\text{range}_{\text{Isefit}}$ 37.5-40.7).) Interestingly, females were more vulnerable for insect bites (p=0.0144).

No other divergent gender characteristics were observed, except that more males went for business trips in both studies ($p_{\text{cohort A}}$=0.0092, $p_{\text{Icohort B}}$=0.0116).

For outcome TD we found in multivariate analysis significant common risk ratios for increasing age (RR A 0.99; 95%CI 0.98-1.00 and B 0.99; 95%CI 0.94-1.00), the Indian subcontinent (RR A 2.55; 95%CI 1.84-33.54 and B 1.54; 95%CI 0.84-2.81), duration of stay (RR A 1.30; 95%CI 1.21-1.39 and B 1.03; 95%CI 1.00-1.07), and constipation (RR A 0.01; 95%CI 0.01-0.05 and B 0.16; 95%CI 0.05-0.48). For cold as outcome we found in the multivariate analysis the following independent risk factors: travel duration (RR A 1.12; 95%CI 0.99-1.27 and B 1.00; 95%CI 0.97-1.04), and fever (RR A 6.13; 95%CI 4.38-8.59 and B 2.34; 95%CI 1.46-3.72).

Physician visits

One third (32.8%) of all cohort A participants either healthy or impaired, reported a MD visit abroad, among cohort B subjects there were one of seven (13.8%), but only TD data was available. When only proportions of those reporting any illness were considered very similar rates for cohort A (13.8%) and cohort B (13.7%) were obtained (hospitalisation excluded). At home 128 (20.8% of any illness) of cohort A and 46 (5.4% of TD cases) of cohort B patients reported doctors' consultation. 41 (4.6%) of cohort B and 14 (1.1%) of cohort A had visited MDs both, at home and abroad.

Incapacitation defined as staying at the hotel room for a minimum of 12 hours or consulting a physician abroad accounted in cohort B to 323 (36.0% of ill ones) confined for a median of 2 days to bed (range 1-14) and 95 (11.2% of TD cases) for cohort A.

For cohort A information regarding IBS and physician visits 6 months post-travel were available 55 (2.2%) visited a MD for any bowel problem and so did 10 of 38 (26.3%) subjects with travel-related Rome III – IBS.

Independent risk factors for visiting a physician included travel duration (RR A 1.26; 95%CI 1.11-1.41 and B 1.08; 95%CI 1.05-1.11), Indian Subcontinent (RR A 1.90; 95%CI 1.14-3.16 and B 1.87; 95%CI 1.13-3.10) and fever (RR A 9.91; 95%CI 6.13-16.12 and B 6.44; 95%CI 4.33-9.57) among subjects of both cohorts each in a logistic multivariate regression subgroup analysis controlled for gender, age and VFR vs. tourists.

DISCUSSION

According to our cohort studies, travellers who mentioned health problems abroad tended to be at the age extremes, young adults and the elderly, stayed longer abroad (maximum of 8 weeks) and had visited more frequently the Indian subcontinent. In addition, the Swiss GeoSentinel data(78) have shown the increased health risk of VFRs abroad with 80% missing pre-travel medical advice. Within cohort A we have found concordant results although VFRs were underrepresented in our travel clinic.

Certain popular tourist destinations, such as Turkey, North Africa and the Caribbean generally observe high travel volumes and TD rates (1, 15) but these visitors are underrepresented in asking for pre-travel medical advice (31), e.g. only 52.1% of responders departing to resource-limited destinations had sought travel health advice at European airports (66).

Diarrhoea was rated in both settings at the top of travel-related syndromes threat(1, 19) with a predominance on the Indian Subcontinent, as was also found in the GeoSentinel network when assessing gastrointestinal infections globally(79, 80) and in other studies (1, 81). Respiratory tract infections are also commonly associated with travel, whereby nonspecific upper respiratory tract infections were most frequently diagnosed with 47.2% including 20.3% of bronchitis(74). The evidence showed that cold symptoms were often linked with fever and influenza infection is known to occur with a two-weeks incidence of 1% among travellers to resource-limited destinations(72). Of note, fever was associated with male gender (RR A 1.36; 1.00-1.84), which is in agreement with the Swiss GeoSentinel data (CID in press) estimating an odds for febrile systemic illness for females of 0.64; 95% CI 0.61-0.67).

Actually, constipation is a rather neglected topic in the travel medicine literature and in pre-travel health consultation. So far, Spanish scientists detected among travellers to Argentina a higher attack rate of constipation of 38% than of diarrhoea (8%)(77). Among our cohorts

lower attack rates were found, 2.3% and 13%, respectively, predominantly among females, but we only collected self reports and defecation frequency for assessing functional constipation(17) was not determined. Changes in diet, time zone, lack of activity while flying or on bus trips, and known side-effects of motility blocking medication are all putative contributing factors. Chang et al. (82) observed among US residents a significant association with analgesics (e.g. seven or more tablets of acetaminophen) excluding IBS symptomatics.

Overall, females were more at risk for constipation and insect bites but they showed better compliance with food hygiene attitudes as well as a lower risk for getting fever or suffering from dysentery.

The two cohort studies were primarily designed to establish in the case of cohort A TD and postinfectious IBS, and in the case of cohort B fever-associated infections. Hence, TD reports in cohort A and fever in cohort B might slightly be overestimated as demonstrates the comparison of these two studies.

The pre-travel advised traveller is known to be health literate (often high educated), vaccinated, maybe hypochondriac, uses more self-medication and needs less physician visits. About 10% of the patients visited a physician abroad and roughly an additional 10% at home, mostly when fever occurred, with longer travel duration or when visiting the Indian subcontinent.

The case series of the GeoSentinel data and the cohort studies share common features, such as to identify (re-)emerging or neglected health problems and to determine travel-related risk factors and populations at special risk, as e.g. age groups, gender, longer stay, travel to the Indian subcontinent. On the other hand, case series usually target more serious health problems or those travellers are unable to cope with alone and ask for a MD diagnosis, often not at a primary care practice(83). Cohort studies, however, are able to provide an overview of the variety of health problems travellers potentially face abroad but for a detailed assessment they usually concentrate on selected health problems for reasons of feasibility. Due to available denominator data the magnitude of a risk can be estimated, e.g. as incidence rate. Therefore, both approaches represent puzzle pieces needed to obtain a complete picture of travel-related health impairments.

Table 1. Comparison of case series and cohort design

Factor	Cohort studies	Case series
Data collection	Prospective	Retrospective
Population	Travellers with pre-travel health advice	Ill returned travellers
Setting	Approximation to travel groups & destinations	Health care
Exposure assessment	Pre- and post-travel	Post-travel
Time frame	Usually limited to months or some years	Potentially long-term
Budget	high	Usually in addition to health insurance
Aim	Overview, risk estimates and risk factors, evaluation of pre-travel health advice, KAPs or health care utilization	Surveillance, risk factors, evaluation of pre-travel health advice
Risk estimates	Relative and absolute, risk ratios, incidence	Relative, odds ratio
Health assessment (outcome)	Usually self-reported, questionnaire-based or serologic	MD diagnosis-based
Spectrum of health problem	All types, usually limited	Usually more severe
Accuracy of health assessment	Case definition based	Guidelines-based, maybe differences by Centres
Bias / confounding	selection bias	selection bias
	information bias	recall bias

Table 2. Demographic and Travel characteristics

	Cohort A Cotravibs N = 2476	**Cohort B Isefit** N = 1450	*p*[a)]	**GeoSentinel Swiss(78)** N = 338
year of study course	2006 – 2008	1998 – 2000		2004 – 2005
Gender percentage of female/	50.8	49.3	0.8947	53.3
male subjects	49.2	50.7		46.7
Age, median (interquartile range)	36 (29-47)	31 (26-43)		32 (32-46)
Travel destinations				
Africa [b)]	808 (32.7)	447 (30.8)	0.5247	70 (20.7)
Asia including India	1105 (44.7)	566 (39.0)	0.1925	82 (24.3)
Indian subcontinent	422 (38.2)	130 (23.0)	0.7600	
Latin America	557 (22.6)	393 (27.1)	0.7774	31 (9.2)
Other	-	44 (3.0)		155 (45.9) [c)]
Duration of stay, median (interq. range)	3 weeks (2-4)	3 weeks (2-5)		15 days (11-24)
Purpose of travel				
Tourism	2093 (87.7)	1197 (82.6)	0.2579	217 (64.2)
VFR	130 (5.5)	102 (7.0)	0.1147	121 (35.8)
Business	163 (6.8)	120 (8.3)	0.4671	14 (4.1)

[a)] Wilcoxon ranksum test for Cotravibs vs. Isefit
[b)] Geosentinel Data contains only subsaharan
[c)] Geosentinel Data contains also Eastern Europe

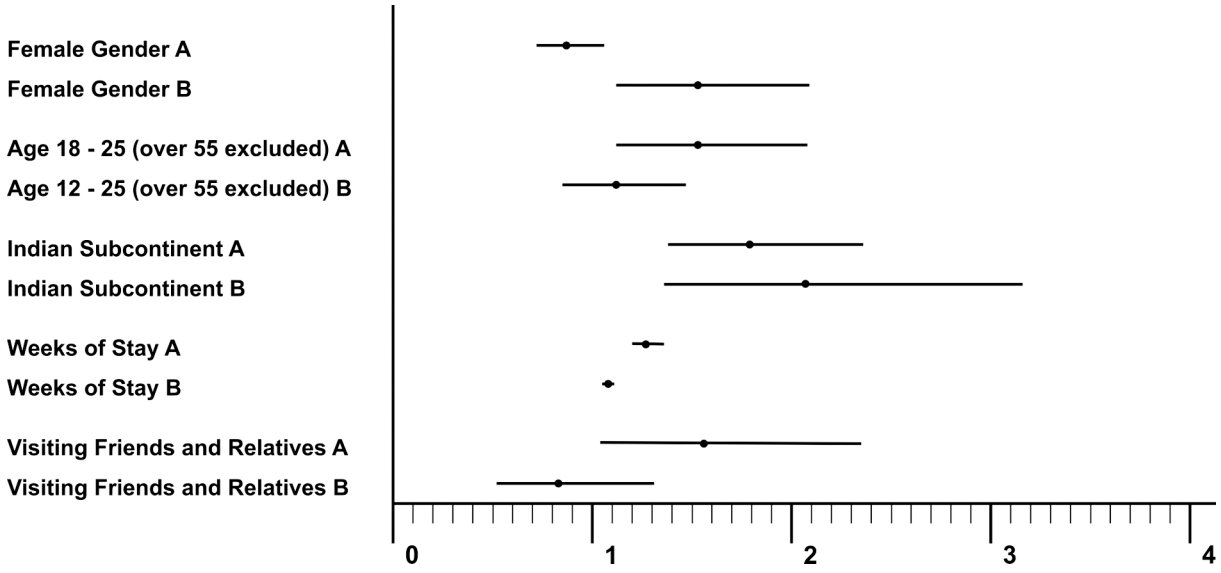
Table 3. Reported Illness during Travel.

	Cotravibs **Cohort A** N = 2476	**Isefit** **Cohort B** N = 1435		***p***	**Hill D.R. et al.(75)** N = 784	**GeoSent (78)** primary symptom N = 670
any	1081 (43.6)		578 (40.3)	0.0462	501 (63.9)	
gastrointestinal						117 (53.9)
diarrhoea	852 (34.4)		375 (25.9)	0.1003	270 (34.4)	79 (18.4)
dysentery	146 (5.9)		164 (11.3)	0.6799	64 (8.2)	
constipation	57 (2.3)		68 (13.0)	0.6040		
respiratory						
cold	254 (10.2)		244 (16.8)	0.1834	204 (26.0)	86 (12.8)
systemic						
measured fever	131 (5.3)		147 (10.1)	0.5593	100 (12.8)	165 (24.6)
dermatological						
skin rash	17 (0.7)		64 (4.4)	0.7112	63 (8.0)	44 (6.6)
other	235 (9.5)[a)]				218 (27.8)	210 (31.3)[c)]
Multiple	239 (9.7)		229 (15.8)	0.3931		
physician visit	*only for TD:*	*only for TD:*	*for any:*		*for any:*	all
abroad	65 (7.6)	58 (6.8)	110 (7.7)	0.4827	59 (7.5)	
at home	53 (6.2)	65 (7.6)		0.4350	93 (11.9)	
hospitalisation abroad	4 (0.2)	4 (0.5)	57 (4.0)		2 (0.3)	

[a)] 94 with headache, 57 with altitude sickness, 44 with arthalgia, 40 other
[b)] gastrointestinal 165 (24.6)
[c)] 92 with head/ear/nose, 47 Musculoskeletal, 37 Fatigue, 34 Other

Figure 1. Legend: Independent relative risk factors for self-reported illness estimated with a multivariate logistic regression analysis

N cohort A=2476 with illness 1081 (43.7%) , N cohort B =1435 with illness 578 (40.3%)



GENERAL DISCUSSION AND OUTLOOK

Our particular traveller-based data report remarkable rates of travellers' diarrhoea (TD any 2-weeks incidence 27%) and a – lower than expected – IBS incidence of 1% within 6 months post-travel. The incidence of IBS in the general population is reported to be 1-3% (84). Our postinfectious IBS incidence rate 6 months post-travel was found to be 3%. Previous traveller-based studies (5, 10, 85) showed, that 4 - 10% of TD patients would develop IBS. Table 1 compares this study with the previous four ones among travellers. They all use the same prospective cohort design with TD as exposure factor but they differ in methods used as i.e. sample size, accurate definition of exclusion criteria and control for potential bias. We excluded any (un-) diagnosed organic and functional gastrointestinal disorder as well as persistent diarrhoea pre-travel. It seems possible that subjects with those pre-morbid gastrointestinal symptoms switched to new IBS cases in these previous studies. Table 2 compares this study with other pIBS studies among community settings. Also the community settings reported higher pIBS incidence rates. Hereby could the characteristics and load of the infectious agent play a role, we had mixed pathogen spectrum with TD, others outbreaks with a single pathogen e.g. *Campylobacter* infection transmitted via regional water supply.

Diarrhoea – whether it might be acquired at home or abroad is the most important risk factor for IBS, furthermore multiple diarrhoeal episodes raise the risk of developing IBS. These findings support the hypothesis that IBS might be a syndrome resulting from a persistent or re-activated low-grade inflammation. Inflammation is associated with production of mediators including prostaglandins, nerve growth factors and 5-hydroxytryptamine. These mediators induce visceral hypersensitivity, exaggerated motor responses, and increased intestinal secretion, which may contribute to episodic diarrhoea (55).

IBS in general might confuse physicians and researches by its multifaceted phenomenon, changing symptoms over time and absence of biological markers. Its diagnostic criteria have been frequently redefined and the present study just started when Rome II switched to Rome III. Rome II required a longer study period of 12 months, which could also be an explanation for our lower incidence rates. Longer study periods partially resulted in increasing incidences (59, 86, 87).

Ideally, more IBS positive cases should have occurred during our study period for deeper analysis. Larger number of individuals could be reached in future by including hospital or health Centre pools, although these patients represent different settings and may used more for case-control studies.

In chapter III we compared prospective cohort study design with the retrospective case series approach. The former represent the best strategy to determine the incidence and natural history of a disorder (in our case TD and IBS), when exposure factors and measurable outcome are clearly defined at the beginning. Figure 2 represents how cohort studies track participants forward in time from exposure to outcome. In figure 3 this scheme was applied to our case.

Our results are a clinically relevant piece of information to medical decision makers and the travellers' community. Every pre-travel consultation has to discuss TD and its management, with special dedication to the risk groups like e.g. diarrhoea susceptible subjects. Reviewing so with visitors of (sub-)tropical destinations the basic TD preventing behaviour, bearing well in mind, that the feasibility in exotic surroundings is restricted (24, 25). Medical experts and travellers should demand for safe food and water supply as well as hygienic infrastructure for lavatories to decrease the diarrhoea burden (49). Discussion of TD management (antibiotic and non-antibiotic) with written instructions for emergency treatment is very useful. Furthermore promising TD vaccines and prophylactic medication are on the way to prevent TD and consequently, postinfectious IBS (88, 89).

	Pitzurra et al.	Stermer et al.	Okhuysen et al.	Illnyckyj et al.
Methods				
study design	prospective cohort of travellers	prospective cohort of travellers	prospective cohort of travellers	prospective cohort of travellers
year of study	2006-2008	2004	2002	1997-1998
Assessment	questionnaires	questionnaires	questionnaires	questionnaires
control group	Yes (unexposed)	Yes (unexposed)	Yes (unexposed)	Yes (unexposed)
exposure	TD, self-reported	TD, self-reported	TD, self-reported	TD,self-reported
follow-up (months)	6	6	6	3
diagnosis criteria	Rome III	Rome II	Rome II	Talley or Rome I
exclusion criteria	• antibiotic prophylaxis • severe chronic illness • previous gastrointestinal surgery • medical/self-reported history of FGID • Rome III for IBS pre-travel fulfilled • recurring diarrhoeal symptoms • pregnancy	• Gastrointestinal history • Rome II for IBS pre-travel fulfilled	• GI history • Rome II (assessment retrospectively, post-travel)	• previous organic bowel disease • or functional bowel disease • chronic GI symptoms • Meeting Rome I or Talley criteria pre-travel
Population				
Recruiting place (country)	Volunteer customers of the Travel Health Centre Zurich	Travel Clinic Bnai Zion Medical Centre Haifa (Israel)	N American students Houston (Texas, USA)	Central civic or private travel clinic & by advertisements (Canada)
Sample size	3420	564	176	198
response rate (n analysed)	72% (2476)	72% (405)	57% (97)	55% (109)
Results				
IBS incidence				
(6m incidence per population at risk)	1.5% (38/2476)	5.7% (23/405)	7.2 (7/97)	2.7% (3/109)
Baseline IBS % (n)	0.7% (12/1624)	2.4% (7/287)	2.7% (1/37)	1.6% (1/61)
pIBS cases % (n)	**3.0% (26/852)**	**14% (16/118)**	**10% (6/60)**	**4.2% (2/48)**

TD cases (attack rate)	852 (34.4%)	118 (29.1%)	61 (63%)	44% (48/109)
lab confirmation	None (sporadic)	5 stool samples	40	none
bacterial etiology	4 spontaneous reports	1 *Campylobacter*	28	
Female gender	50.8%	46.7%	50.5%	55.5%
Age, mean (range)	39 (18-82)	30.8 (range not provided)	not provided (students)	45 (18-73)
Destinations	resource-limited & high TD risk 45% Asia 33% Africa 22% Latin America	84% Asia 5% Africa and S-America	100% Mexico	outside US or Canada 15% Mexico 7% India 6% Cuba
Travel duration	21d (1-12 weeks)	32d (14-180 days)	5 weeks	19d (5-70)
lab confirmation	None (sporadic)	5 stool samples	40	none
bacterial etiology	4 spontaneous reports	1 *Campylobacter*	28	

Table 1. *Characteristics of IBS-studies among travellers*.

Table 2. *Postinfectious IBS incidence rates among various settings. Adapted to (9)*

Author, year of publication	percentage with pIBS	follow-up period (mth)	No. infected	organism	setting
Marshall et al, 2006	36	24	464	*C jejuni* + E coli O157	Community[1)]
McKendrick and Read, 1994	31	12	38	S enteritidis	Elderly care[1)]
Gwee et al, 1996	29	3	75	Mixed bacterial	Infectious diseases hospital
Marshall et al, 2007	24	3	109	Norovirus	Travellers[1)]
Soyturk et al, 2007	14	6	72	*Trichinella britovi*	Community
Dunlop et al, 2003	13	6	747	C jejuni	Community
Mearin et al, 2005	11.6	12	677	*Salmonella*	Community[1)]
Moss-Morris and Spence, 2006	11	6	748	*C jejuni* and EBV	Community
Thorley et al, 2001	9	6	180	*C jejuni*	Community
Wang et al, 2004	8	12-24	295	*Shigella* spp	Community[1)]
Marshall et al, 2007	7.9	6	260	*C jejuni*	Community
Ji et al, 2005	7	6	101	*Shigella* spp	Community[1)]
Dizdar et al, 2007	7	12	1300	*Giardia duodenalis*	Community[1)]
Neal et al, 1997	7	6	390	Mixed bacterial	Community
Borgaonkar et al, 2006	3.7	3	231	Mixed	Community
Pitzurra et al, 2010	3.0	6	852	Mixed, TD	Travellers

NOTE. There is a wide range of percentages developing pIBS that appears to be related to the type of organism. [1)] Outbreak of infectious diarrhoea.

Figure 2. *Schematic diagram of concurrent, retrospective, and ambidirectional cohort studies.(90)*

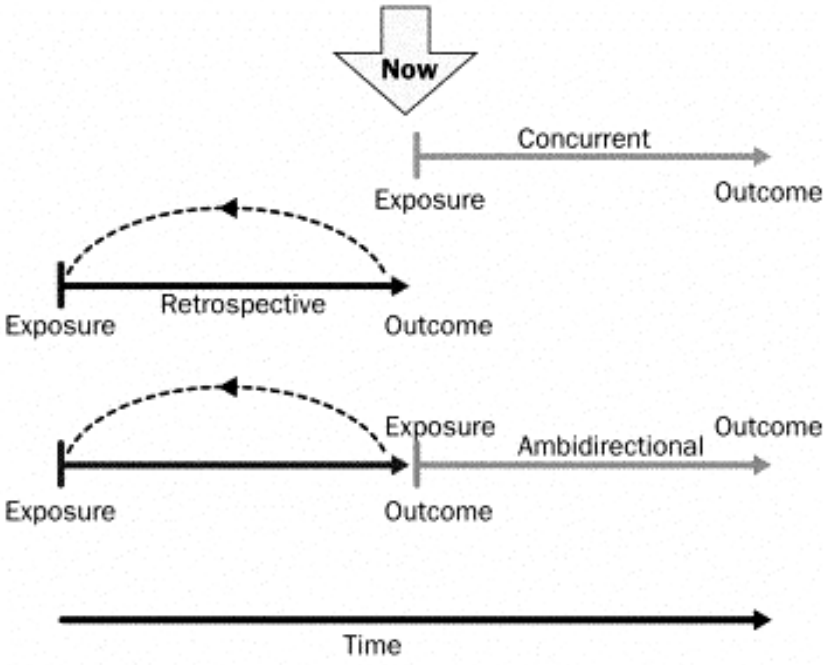
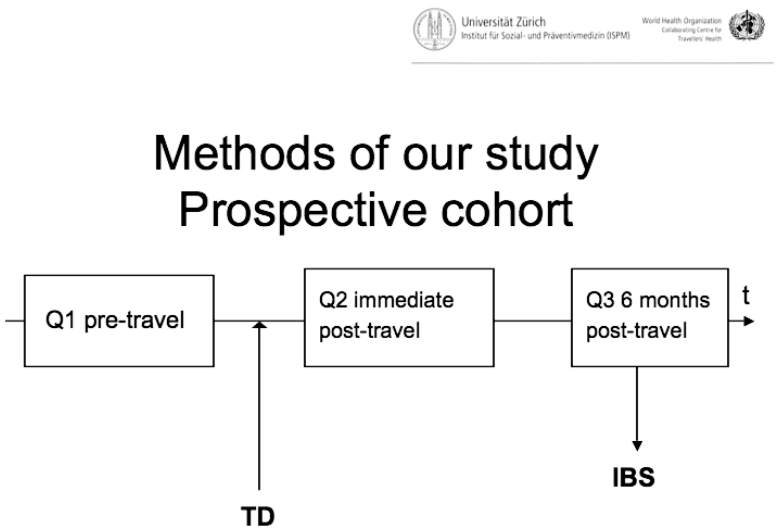


Figure 3. *Our prospective cohort study design with questionnaires (Q), Travellers' Diarrhoea (TD) as exposure factor and Irritable Bowel Syndrome (IBS) as outco*



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APPENDIX

Informed Consent and Questionnaires

Universität Zürich
Zentrum für Reisemedizin

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Wissenschaftliche Studie zu Reisedurchfall und dessen Folgen

Reisedurchfall tritt in Entwicklungsländern häufig auf. Wenig bekannt ist, dass dieses lästige Übel gelegentlich zu chronischen Darmstörungen führen kann, welche über Monate oder Jahre anhalten. Um festzustellen, wo und wie häufig mit derartigen langwierigen Problemen zu rechnen ist, laden wir Sie ein, an einer Studie teilzunehmen.
Diese ist im Wesentlichen auf drei kurze Fragebogen beschränkt.

STUDIENABLAUF
Wenn Sie beitragen wollen, Reisende künftig noch besser informieren und beraten zu können, so beantworten Sie doch bitte hier in der Wartezeit nachfolgende Fragen.

Auf die Reise erhalten Sie einen kurzen Fragebogen und einen weiteren kurz nach Ihrer Heimkehr. Letztes Frageformular bitten wir Sie 6 Monate später auszufüllen. Teilen Sie uns bitte mit, wenn sich Ihre Adresse ändern sollte.

Sollten sie nach 6 Monaten tatsächlich noch an Darmstörungen leiden, so bieten wir Ihnen unentgeltlich eine *Beratung durch Darmspezialisten* im Universitätsspital Zürich an — gemeinsam werden Sie bestimmen, ob weitere Abklärungen angebracht sind. Daraus allenfalls resultierende Kosten sind krankenkassenpflichtig.

Gesundheitsrisiken erwachsen Ihnen aus dieser Studie nicht, da im Verlauf der Studie weder Laboruntersuchungen stattfinden noch Sie irgendein Medikament erhalten — wir bitten Sie lediglich, etwas Zeit zu investieren.

Teilen Sie uns bitte mit, falls Sie je Komplikationen oder Operationen im Magen-Darm-Trakt hatten. Selbstverständlich werden alle Daten anonym ausgewertet und jederzeit können Sie ohne Angaben von Gründen auf die weitere Teilnahme an der Studie verzichten. Sie können uns auch angeben, ob Sie wünschen, dass wir Ihnen einen Kurzbericht zustellen.

Ihre Teilnahme und Ihre Zufriedenheit ist uns wichtig! Haben Sie Fragen noch bezüglich Durchfall und neuesten Stand seiner Medikation?
Unter denjenigen, welche uns auch den letzten Fragebogen Q3 (nach 6 Monaten) zurücksenden, *verlosen wir Reisegutscheine* (1 x 1000 CHF, 4 x 500 CHF)sowie Gutscheine für eine *reisemedizinische Beratung* (15 x 200 CHF).
Zudem können Sie sich vor Ihrer nächsten Reise telefonisch einen Termin für eine reisemedizinische Beratung reservieren (während der offiziellen Beratungszeiten) und werden dann ohne Wartezeit beraten!

EINVERSTÄNDNIS

Ich willige ein, an der Studie "Reisedurchfall und deren Folgen" teilzunehmen — allfällige Fragen konnte ich mit dem Team des Zentrums für Reisemedizin der Universität Zürich besprechen.

Name/Vorname (Druckschrift) : _____

email (*reminder, kein Spam*) : _____

☎ (wichtige Nachfragen) : _____

Datum Unterschrift _____

Unterschrift Studienteam

Datum Unterschrift _____

Eintrittsfragebogen Q1

Datum: ID – Nr.

1. Litten Sie je über mehrere Monate an Unwohlsein oder Schmerzen im Bauch (an mindestens zwei Tagen pro Woche)? *(Menstruationsbeschwerden ausgenommen)*

❑ NEIN ⟹ **weiter zu Frage 8.** ❑ JA ⇓ weiter zu Frage 2.

2. Besserten sich das Unwohlsein oder die Schmerzen nach dem Stuhlgang oder hörten sie ganz auf?

❑ NEIN ❑ JA

3. Als das Unwohlsein oder die Schmerzen begonnen haben, hat sich die Häufigkeit Ihres Stuhlganges verändert (entweder häufiger oder seltener Stuhlgang)?

❑ NEIN ❑ JA

4. Als das Unwohlsein oder die Schmerzen begonnen haben, hatten Sie anderen (eher weicheren oder härteren) Stuhl festgestellt als üblicherweise?

❑ NEIN ❑ JA

5. Traten in den vergangenen 6 Monaten während mindestens 6 Wochen (mindestens an einem Tag pro Woche) eines der folgenden Symptome auf?

Bitte alles Zutreffende ankreuzen.

❑ Stuhlgang weniger als dreimal pro Woche

❑ Stuhlgang häufiger als dreimal pro TAG (4 mal oder mehr)

❑ harter oder klumpiger Stuhl

❑ wässriger, ungeformter oder breiartiger Stuhl

❑ Krämpfe während des Stuhlganges

❑ Gefühl einer unvollständigen Entleerung nach dem Stuhlgang

❑ Völlegefühl, Blähung oder Anschwellen im Unterbauch

❑ Ein Gefühl, dass der Stuhl während des Stuhlganges blockiert ist

❑ Ein Bedürfnis, mit Druck eine vollständige Stuhlentleerung erreichen zu müssen

6. Wurde ein „nervöser Darm“, bzw. ein „Reizdarm-Syndrom“ je durch einen Arzt bestätigt?

❑ JA, durch den Arzt bestätigt ❑ NEIN, ich war deswegen nie beim Arzt

7. Was wurde vom Arzt als Ursache der Beschwerden beziehungsweise des „Reizdarms“ angenommen?

❑ frühere Reisen

❑ Arzt wusste keine Erklärung oder hat keine Ursache genannt

❑ ich habe keinen Arzt befragt

❑ ich weiss nicht

❑ Anderes, was? _____

8. Wurde in Ihrer Familie, bei Eltern, Geschwistern oder eigenen Kindern, je ein Reizdarm von einem Arzt festgestellt?

❑ NEIN ❑ JA

9. Wie anfällig stufen Sie sich in Bezug auf Durchfall ein?

❑ sehr anfällig ❑ mässig anfällig ❑ gar nicht anfällig

10. Haben Sie in den letzten vier Monaten je an Durchfall gelitten?

❑ JA ⇓ ❑ NEIN ⇒ **weiter zu Frage 15.**

11. Wieviele Stuhlentleerungen hatten Sie maximal pro 24 Stunden?

____ Stuhlentleerungen ❑ weiss nicht mehr

12. Wie war dabei die Stuhlkonsistenz vorwiegend?

❑ wässrig ❑ breiig ❑ geformt

13. Hatten Sie zusammen mit dem Durchfall eine oder mehrere der folgenden Beschwerden:

❑ Fieber ❑ Übelkeit ❑ Erbrechen ❑ Bauchkrämpfe

❑ plötzlicher Stuhldrang ❑ Blut im Stuhl ❑ Schleim im Stuhl

❑ Keine Begleit-Beschwerden

14. Wieviele Tage hat der Durchfall insgesamt etwa angedauert?

❑ etwa __ Tage ❑ dauert noch an ❑ weiss nicht mehr

15. Haben Sie schon während oder nach einer **früheren Reise** an „Reisedurchfall“ gelitten?

❑ NEIN ⇒ weiter zu Frage 17. ❑ JA ❑ weiss nicht mehr

16. Wie beurteilen Sie den Schweregrad des Reisedurchfalles?

❑ leicht (ich konnte die geplanten Tätigkeiten immer durchführen)

❑ mittel (ich konnte nicht alle Tätigkeiten durchführen)

❑ schwer (ich musste mindestens 12 Stunden zuhause bleiben oder konsultierte einen Arzt)

17. Wurde je von einem Arzt eine chronische Darmerkrankung festgestellt, z.B. Darmkrebs, entzündliche Darmerkrankung (Morbus Crohn, Colitis ulcerosa), Zöliakie?

❑ NEIN ⇓ ❑ JA ⇒ STOP! Wenden Sie sich bitte an das Studienteam

18. Leiden Sie an einer anderen chronischen Erkrankung?

❑ NEIN ⇓ ❑ JA, welche?

❑ rheumatischer Formenkreis 18.1

❑ Diabetes mellitus/Zuckerkrankheit 18.2

❑ Herz-, Kreislauf (z.B. Bluthockdruck) 18.3

❑ Venenthrombosen 18.4

❑ Atemwegserkrankung *(Asthma she. unten)* 18.5

❑ Schilddrüsenerkrankung 18.6
(z.B. Morbus Basedow, Kropf)

❑ Gicht 18.7

❑ andere, welche? _____ 18.8

19. Leiden Sie an einer allergischen Erkrankung?

❑ JA ❑ NEIN ⇒ **weiter zu Frage 21.**

Wenn JA, an welcher? *Mehrfachantworten sind möglich.*

❑ Heuschnupfen

❑ Atopische Dermatitis oder Neurodermitis

❑ Allergisches Asthma

❑ Bienen- und Wespenstichallergie

❑ Anderes, was? _____

20. Wurde diese allergische Erkrankung durch einen Arzt bestätigt?

❑ NEIN ❑ JA

21. Haben Sie in den letzten zwölf Monaten ein einschneidendes Ereignis erlebt? (z.B. schwerer Unfall, Todesfall in der engeren Familie, Scheidung, Arbeitsplatz-Verlust)

❑ NEIN ❑ JA, welches? _____

22. Stehen Sie im Moment unter Stress / starker Belastung?

❑ überhaupt nicht ❑ wenig ❑ mittelmässig ❑ stark

23. Rauchen Sie, wenn auch nur selten (Zigaretten, Zigarren, Cigarillos, Pfeife)?

❑ NEIN ❑ JA

Wenn JA, wie viel rauchen Sie im Durchschnitt?

❑ weniger als einmal täglich

❑ einmal täglich ❑ mehrmals täglich

24. Haben Sie je regelmässig während mehr als 6 Monaten geraucht?

❑ NEIN ❑ JA

25. Trinken Sie täglich **alkoholische** Getränke?

❑ NEIN ❑ JA

Wenn JA, trinken Sie täglich mehr als einen halben Liter Bier oder ein Glas Wein oder ein Glas gebranntes Wasser (wie z.B. Schnaps)?

❑ NEIN ❑ JA

26. In welchem Land wurden Sie geboren
oder lebten als Kind während mindestens fünf Jahren?

❑ CH ❑ anderes Land: _____

27. Welches ist die höchste Ausbildung, die Sie mit einem Diplom oder Zeugnis abgeschlossen haben?

- ❑ Obligatorische Schule oder kürzere Schulzeit
- ❑ Berufslehre, Berufsschule
- ❑ Maturitätsschule, Lehrerseminar, andere allgemeinbildende Schule
- ❑ Höhere Berufsausbildung (Meisterdiplom, Eidg. Fachausweis)
- ❑ Universität, Hochschule oder Fachhochschule
- ❑ Andere Ausbildung, welche?_____
- ❑ Keine Ausbildung

28. Wird dies Ihre erste Reise sein:

- ❑ in diesen Teil der Erde (Sub-Kontinent)
- ❑ in ein tropisches oder subtropisches Land
- ❑ NEIN

29. Welches ist Ihre Körpergrösse? _____ cm

30. Welches ist Ihr Körpergewicht? _____ kg

HERZLICHEN DANK FÜR IHRE TEILNAHME!

Bitte geben Sie diesen Bogen der studienverantwortlichen Person ab

Q2A Reisedurchfall unterwegs

Datum: ID – Nr.

Bitte auf Reise mitnehmen! Sofern Sie während Ihrer Reise an Durchfall leiden, bitten wir Sie, diesen Fragebogen baldmöglichst auszufüllen und uns sobald Sie zurück sind zuzusenden. Auch wenn Sie keinen Durchfall während Ihrer Reise hatten, möchten wir Sie bitten, die Fragen zu beantworten und uns baldmöglichst mit beiliegendem Antwortcouvert zuzusenden. Herzlichen Dank!

Bitte das zutreffende Feld ❑ ankreuzen oder hineinschreiben bei ____ .

1. Sind Sie wie geplant **für** ____ **Wochen nach** _____ **gereist?**

- ❑ JA
- ❑ NEIN,
- ❑ ich bin stattdessen für ____ Wochen nach _____ gereist.

❑ ich bin nicht gereist. ⇒ **für Sie ist die Befragung zu Ende, vielen Dank.**

2. Haben Sie unterwegs (oder kurz nach Ihrer Rückkehr) Durchfall erlitten?

❑ JA ⇓ ❑ NEIN ⇒ **weiter zu Frage 10.**

3. Wieviele Stuhlentleerungen hatten Sie maximal pro 24 Stunden?

___ Stuhlentleerungen

2.1. Haben Sie während (oder kurz nach) Ihrer Reise **mehrere** Durchfall*erkrankungen* gehabt, wobei jeweils mindestens 3 Tage (mind. 72 h) dazwischen lagen?

❑ JA, wie viele Male?
- ❑ zweimal
- ❑ dreimal
- ❑ anderes, was? _____

❑ NEIN, nur einmal Durchfall*erkrankung* gehabt.

4. Wie war dabei die Stuhlkonsistenz vorwiegend?

❑ wässrig ❑ breiig ❑ geformt

5. Hatten Sie zusammen mit dem Durchfall eine oder mehrere der folgenden Beschwerden:

❑ Fieber ❑ Übelkeit ❑ Erbrechen ❑ Bauchkrämpfe

❑ plötzlicher Stuhldrang ❑ Blut im Stuhl ❑ Schleim im Stuhl ❑ Keine Begleit-Beschwerden

6. Am wievielten Tag nach Ihrer Ankunft am Urlaubsort ist der Durchfall aufgetreten?

❑ am __. Tag ❑ in der ___. Woche ❑ weiss nicht mehr

7. Wieviele Tage hat der Durchfall insgesamt etwa angedauert?

❑ etwa __ Tage ❑ dauert noch an ❑ weiss nicht mehr

8. Wie beurteilen Sie den Schweregrad des Durchfalles?

❑ leicht (ich konnte die geplanten Tätigkeiten immer durchführen)

❑ mittel (ich konnte nicht alle Pläne durchführen)

❑ schwer (ich musste mindestens 12 Stunden im Zimmer bleiben oder konsultierte einen Arzt)

9. Haben Sie wegen des Durchfalls im Ausland: *mehrere Antworten möglich*

❑ Medikamente in einer Apotheke vor Ort besorgt?

❑ einen Arzt konsultiert? Falls JA:
- ❑ in der Praxis
- ❑ im Spital (mindestens eine Nacht)
- ❑ einen bekannten Arzt, z.B. in der Reisegruppe

❑ Anderes, was? _____

❑ Arzt nach der Reise konsultiert, Stuhlbefund? : _____

10. Haben Sie ein Durchfall-Medikament eingenommen?

❑ NEIN ❑ JA, welches? _____

wofür? *zur Behandlung von Symptomen, nämlich*

❑ durchfallstoppendes Medikament

❑ Flüssigkeitsersatz (rehydrierende Lösung)

❑ vorbeugend (präventiv) gegen Durchfall

❑ weiss nicht mehr

11. Sind Sie während dieser Reise oder kurz nach Ihrer Rückkehr erkrankt?

*(Unfälle **nicht** eingeschlossen*)

❑ NEIN ⇒ **weiter zu Frage 12.**

❑ JA, hatten Sie Fieber? ❑ NEIN

❑ JA, Temperatur gemessen: ____ °C

Sind andere Symptome aufgetreten?

❑ Erkältung (Halsschmerz, Husten) 11.1

❑ Gelenkschmerzen 11.2

❑ Hautausschlag (nicht Sonnenbrand) 11.3

❑ Kopfschmerzen, Schwindel (wegen Höhe) 11.4

❑ Lähmungserscheinungen 11.5

❑ Verstopfung 11.6

❑ anderes, was? _____ 11.7

12. Haben Sie während Ihrer Reise irgendwelche andere Medikamente eingenommen?

❑ NEIN ❑ JA, gegen? _____

Name? _____ wie lange?_____

13. Haben Sie ein **Antibiotikum** eingenommen?

❑ NEIN ❑ JA, welches? _____

wofür? *zur Behandlung von Symptomen, nämlich bei*

- ❑ Durchfall
- ❑ andere Magen-Darm-Erkrankungen
- ❑ andere Infektionen
- ❑ vorbeugend (präventiv) gegen Durchfall
- ❑ weiss nicht mehr

14. Folgten Sie der Empfehlung „***cook it, boil it, peel it or forget it***“ (koch es, schäl es oder vergiss es!)?

❑ JA ❑ NEIN ❑ ich kenne die Empfehlung nicht

15. Wo haben Sie sich verpflegt? *mehrere Antworten möglich*

- ❑ privat (z.B. bei einer Familie, selber gekocht)
- ❑ am Buffet in Hotels, Restaurants
- ❑ bei Strassenverkäufern

16. Haben Sie Leitungswasser getrunken?

❑ NEIN ❑ JA

17. War die medizinische Reiseberatung für Sie von Nutzen?

❑ sehr nützlich ❑ mässig nützlich ❑ gar nicht nützlich

Was haben Sie an der Beratung vermisst?

HERZLICHEN DANK FÜR IHRE TEILNAHME!

Bitte in beiliegendem Couvert zurücksenden

Wir melden uns bei Ihnen für die Studie in **6** Monaten dann automatisch wieder.
Teilen Sie uns bitte mit, sollten sich Ihre Adressdaten ändern.

Q3 Ihr Befinden 6 Monate nach der Reise Datum: ID-Nr.:

1. Haben Sie während der letzten 6 Monate ein *zweites* Mal ein tropisches oder subtropisches Land oder ein Entwicklungsland besucht?

❑ NEIN

❑ JA, wann (Datum)? Von: _____ bis: _____

Reiseziel(e)? _____ Wie lange dauerte die Reise? _____ Wochen

2. Litten Sie während der vergangenen 6 Monate nach Ihrer Rückkehr an Durchfall?
Mehrfachantworten möglich

❑ NEIN ❑ JA, wann?

❑ während der unter 1. erwähnten Reise, wie lange? ___ Tage

❑ zu Hause, wann? __ / __ / __, wie lange? ___ Tage

❑ anderes, was? _____

3. Litten Sie in den vergangenen **3 Monaten** an *mindestens* **zwei Tagen pro Monat** d.h. wiederholt an Unwohlsein oder Schmerzen am Unterbauch?

(Menstruationsbeschwerden ausgenommen)

❑ NEIN

⇒ **weiter zu Frage 11.**

❑ JA, *mehrere Antworten möglich:*

❑ JA, im 1. bis 3. Monat nach der ersten Reise

❑ JA, im 4. bis 6. Monat nach der ersten Reise

4. Besserten sich das Unwohlsein oder die Schmerzen nach dem Stuhlgang oder hörten Sie ganz auf?

❑ NEIN ❑ JA

5. Als das Unwohlsein oder die Schmerzen begonnen haben, hatten Sie <u>selteneren</u> Stuhlgang?

❑ NEIN ❑ JA

6. Als das Unwohlsein oder die Schmerzen begonnen haben, hatten Sie <u>häufigeren</u> Stuhlgang?

❑ NEIN ❑ JA

7. Als das Unwohlsein oder die Schmerzen begonnen haben, hatten Sie eher weicheren Stuhl festgestellt als üblicherweise?

❑ NEIN ❑ JA

8. Als das Unwohlsein oder die Schmerzen begonnen haben, hatten Sie eher härteren Stuhl festgestellt als üblicherweise?

❑ NEIN ❑ JA

9. Traten in den vergangenen **6** Monaten während *mindestens 6 Wochen* (mindestens 2 bis 3 mal pro Monat) eines der folgenden Symptome auf?

Bitte alles Zutreffende ankreuzen.

- ❑ Stuhlgang weniger als dreimal pro Woche
- ❑ harter oder klumpiger Stuhl
- ❑ Krämpfe während des Stuhlganges
- ❑ Gefühl einer unvollständigen Entleerung nach dem Stuhlgang
- ❑ Ein Gefühl, dass der Stuhl während des Stuhlganges blockiert ist
- ❑ Ein Bedürfnis mit Druck, eine vollständige Stuhlentleerung erreichen zu müssen
- ❑ wässriger, ungeformter oder breiartiger Stuhl
- ❑ Stuhlgang häufiger als dreimal pro TAG (4 mal und mehr)
- ❑ Völlegefühl, Blähung oder Anschwellen

10. Wie häufig traten in den vergangenen **3** Monaten

	nie oder selten	manchmal	oft	fast immer	immer
• harter oder klumpiger Stuhl auf?	❑	❑	❑	❑	❑
• ungeformter, wässriger oder breiartiger Stuhl auf?	❑	❑	❑	❑	❑

11. Traten in den vergangenen 6 Monaten während *mindestens* 6 Wochen (mindestens an einem Tag pro Woche) Unwohlsein oder Schmerzen im Bauch oberhalb des Bauchnabels *(aber nicht in der Brust)* auf?

❑ NEIN ⇒ **weiter zu Frage 13.** ❑ JA

12. Besserten sich das Unwohlsein oder die Schmerzen im Bauch oberhalb des Bauchnabels *(aber nicht in der Brust)* nach der Stuhlentleerung?

❑ NEIN ❑ JA

13. Haben Sie wegen der oben genannten Beschwerden je irgendwelche Medikamente eingenommen?

❑ NEIN

❑ JA, gegen?_____ Name? _____ wie lange?_____

14. Haben Sie wegen der oben genannten Beschwerden je einen Arzt aufgesucht?

❑ NEIN ⇒ **Ende der Befragung, vielen Dank!**

❑ JA, welches war sein Befund? _____

15. Dürfen wir den Arzt kontaktieren - ausschliesslich zur Diagnose des Reizdarmes

❑ NEIN ❑ JA: Name, Vorname: _____

Strasse: _____

Postleitzahl, Ort: _____ _____

Telefon: _____

HERZLICHEN DANK FÜR IHRE TEILNAHME!

Bitte in beiliegendem Couvert zurücksenden

CURRICULUM VITAE

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Scientific Contributions

Articles

Pitzurra R, Mutsch M, Steffen R. Travellers' Diarrhoea. Der Gastroenterologe. 2007 Apr 2;161-169

Oral Presentations

Pitzurra R, Tschopp A. Hatz C, Steffen R. Mutsch M. Irritable Bowel Syndrome among a Cohort of European Travellers to Low Income Destinations. 11th Conference of the International Society of Travel Medicine. Budapest. 26 May 2009

Pitzurra R. *Montezumas Rache*. Colloquium Institute of Social and Preventive Medicine. University of Zurich. Apr 2008

Poster Presentations

Hatz C. Irritable Bowel Syndrome among a Cohort of European Travellers to Low Income Destinations. European Congress of Clinical Microbiology and Infectious Diseases. Helsinki.16 May 2009

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